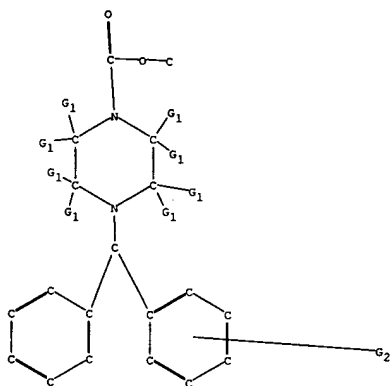
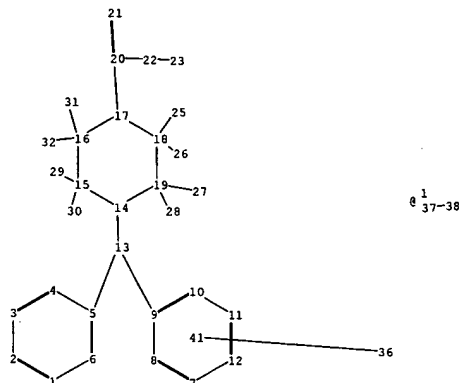


Broodn Pucy.

e 1  
O-Ce 1  
37-38

chain nodes :

13 20 21 22 23 25 26 27 28 29 30 31 32 36 37 38

ring nodes :

1 2 3 4 5 6 7 8 9 10 11 12 14 15 16 17 18 19

chain bonds :

5-13 9-13 13-14 15-29 15-30 16-31 16-32 17-20 18-25 18-26 19-27 19-28 20-21  
20-22 22-23 37-38

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12 14-15 14-19 15-16  
16-17 17-18 18-19

exact/norm bonds :

13-14 14-15 14-19 15-16 15-29 15-30 16-17 16-31 16-32 17-18 17-20 18-19 18-25  
18-26 19-27 19-28 20-21 20-22 22-23 37-38

exact bonds :

5-13 9-13

normalized bonds :

1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12

isolated ring systems :

containing 14 :

G1:H,CH3

G2:X,Ak,[\*1]

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom  
 12:Atom 13:CLASS 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 20:CLASS  
 21:CLASS 22:CLASS 23:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS 30:CLASS  
 31:CLASS 32:CLASS 36:CLASS 37:CLASS 38:CLASS 41:CLASS

10/076448

=>

Uploading 10076448.str

L4           STRUCTURE UPLOADED

=> s 14

SAMPLE SEARCH INITIATED 17:55:08 FILE 'REGISTRY'  
SAMPLE SCREEN SEARCH COMPLETED -       19 TO ITERATE

100.0% PROCESSED           19 ITERATIONS                   4 ANSWERS  
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:   ONLINE   \*\*COMPLETE\*\*  
                          BATCH    \*\*COMPLETE\*\*  
PROJECTED ITERATIONS:           119 TO       641  
PROJECTED ANSWERS:               4 TO        200

L5           4 SEA SSS SAM L4

=> s 14 sss full

FULL SEARCH INITIATED 17:55:17 FILE 'REGISTRY'  
FULL SCREEN SEARCH COMPLETED -       325 TO ITERATE

100.0% PROCESSED           325 ITERATIONS                  43 ANSWERS  
SEARCH TIME: 00.00.02

L6           43 SEA SSS FUL L4

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	166.31	166.52

FILE 'CAPLUS' ENTERED AT 17:55:26 ON 02 JUN 2003  
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FILE COVERS 1907 - 2 Jun 2003   VOL 138 ISS 23  
FILE LAST UPDATED: 1 Jun 2003   (20030601/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 16

L7           20 L6

=> d 17 1-20 bib abs hitstr

10/076448

10/076448

L7 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2003 ACS

AN 2003:221676 CAPLUS

DN 138:255252

TI Preparation of substituted 1-benzhydryl-4-[2-(4-piperidinyl)acetyl]-piperazines as 17-.beta.-hydroxysteroid dehydrogenase type 3 inhibitors for the treatment of androgen dependent diseases

IN Guzi, Timothy J.; Paruch, Kamil; Mallams, Alan K.; Rivera, Jocelyn D.; Doll, Ronald J.; Girijavallabhan, Viyyoor M.; Pachter, Jonathan; Liu, Yi-Tsung; Saksena, Anil K.

PA Schering Corporation, USA

SO PCT Int. Appl., 291 pp.

CODEN: PIXXD2

DT Patent

LA English

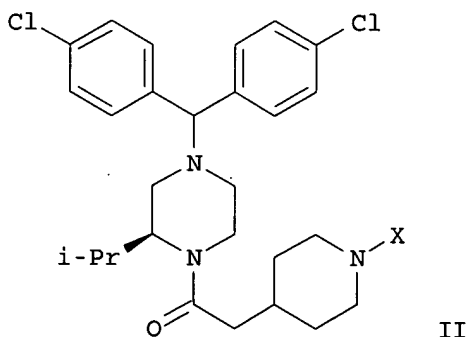
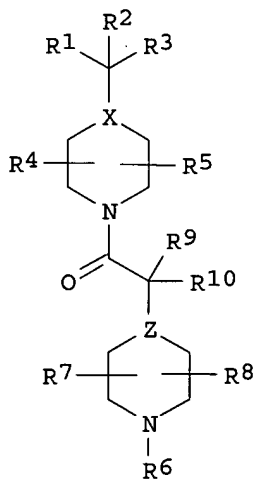
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003022835	A1	20030320	WO 2002-US28181	20020905
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRAI US 2001-317715P P 20010906

OS MARPAT 138:255252

GI



AB The title compds. [I; R1, R2 = (un)substituted (hetero)aryl, (hetero)aryllakyl; R3 = H, OH, alkoxy, alkyl, provided that when X = N, R3 is not OH or alkoxy; R4, R5, R7, R8 = H, OH, alkyl, etc.; R6 = COR15, SO2R15; R9, R10 = H, F, CF3, etc.; R15 = alkyl, cycloalkyl, aryl, etc.; X, Z = C, N] which are useful as inhibitors of Type 3 17.beta.-hydroxysteroid dehydrogenase, were prepd. Thus, treating the amine II.2HCl [X = H] (multi-step synthesis given) with TMSNCO in the presence of TEA in CH2Cl2

10/076448

afforded 61% II [X = CONH2]. Compds. I have a range of 17.β.-hydrosteroid dehydrogenase type 3 binding activity from about 0.005 nM to about > 100 nM.

IT 502486-90-0P 502486-93-3P 502486-95-5P

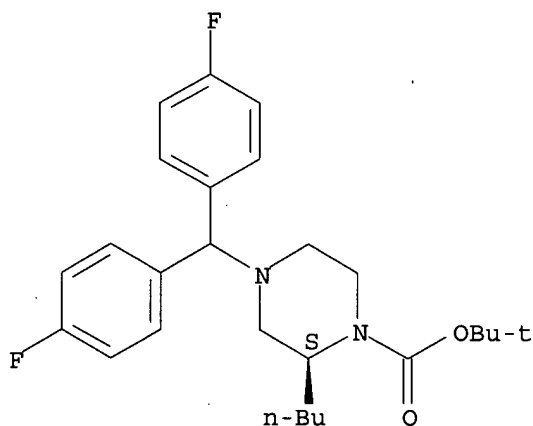
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of substituted 1-benzhydryl-4-[2-(4-piperidinyl)acetyl]-piperazines as 17-β.-hydroxysteroid dehydrogenase type 3 inhibitors for the treatment of androgen dependent diseases)

RN 502486-90-0 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[bis(4-fluorophenyl)methyl]-2-butyl-, 1,1-dimethylethyl ester, (2S)- (9CI) (CA INDEX NAME)

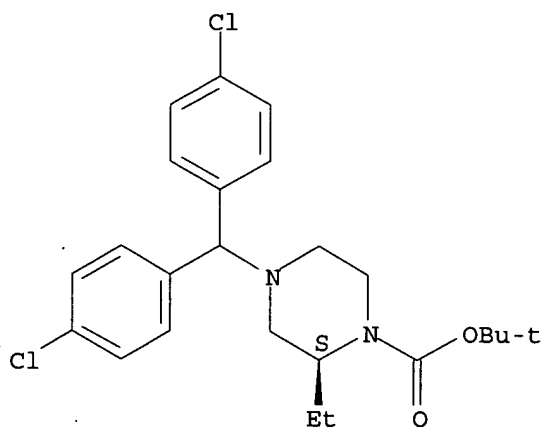
Absolute stereochemistry.



RN 502486-93-3 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[bis(4-chlorophenyl)methyl]-2-ethyl-, 1,1-dimethylethyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

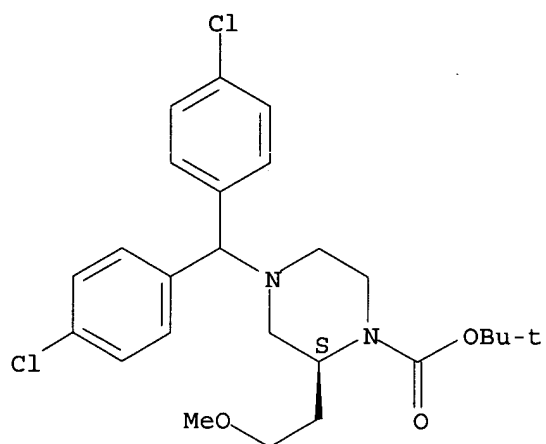


RN 502486-95-5 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[bis(4-chlorophenyl)methyl]-2-(2-methoxyethyl)-, 1,1-dimethylethyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

10/076448



RE.CNT 3      THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/076448

L7 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 2002:906172 CAPLUS  
DN 138:4616  
TI Preparation of 4-(phenyl-piperazinyl-methyl)-benzamides as .delta. opioid  
receptor agonists for the treatment of pain, anxiety or gastrointestinal  
disorders  
IN Brown, William; Walpole, Christopher; Plobeck, Niklas  
PA Astrazeneca Ab, Swed.  
SO PCT Int. Appl., 40 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002094794	A1	20021128	WO 2002-SE956	20020516
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
PRAI	SE 2001-1772	A	20010518		
	SE 2001-3820	A	20011115		
OS	CASREACT 138:4616; MARPAT 138:4616				
GI					

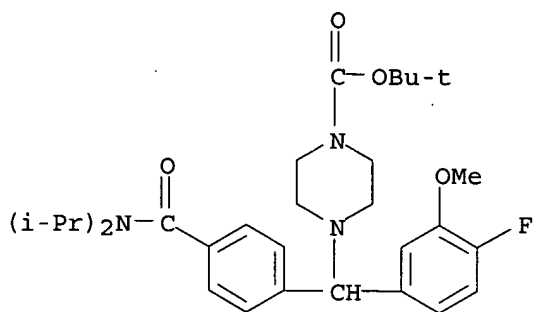
\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The title compds. [I; R1 = (un)substituted Ph, pyridyl, thienyl, furanyl, imidazolyl, pyrrolyl, triazolyl, thiazolyl, and pyridyl N-oxide; R2 = Et, iso-Pr; R3 = H, F; R4 = OH, NH2, NHSO2R5; R5 = H, CF3, alkyl] and their salts, useful in therapy, in particular in the management of pain, anxiety and functional gastrointestinal disorders, were prepd. and formulated. Thus, N-alkylation of the benzamide II (2-step synthesis given) with PhCH2Br followed by treatment of the intermediate with BBr3 in CH2Cl2 afforded 50% I.TFA [R1 = Ph; R2 = iso-Pr; R3 = F; R4 = OH]. The exemplified compds. I showed IC50 of 0.50-13 nM against .delta. receptor binding.

IT 477191-68-7P 477191-73-4P 477191-75-6P  
477191-76-7P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(prepn. of 4-(phenyl-piperazinyl-methyl)-benzamides as .delta. opioid receptor agonists for treating pain, anxiety or gastrointestinal disorders)

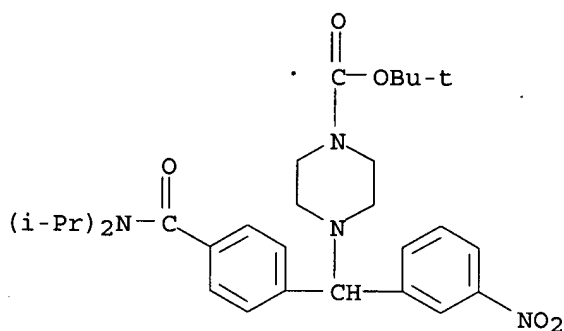
RN 477191-68-7 CAPLUS  
CN 1-Piperazinecarboxylic acid, 4-[[[4-[[bis(1-methylethyl)amino]carbonyl]phenyl](4-fluoro-3-methoxyphenyl)methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

10/076448



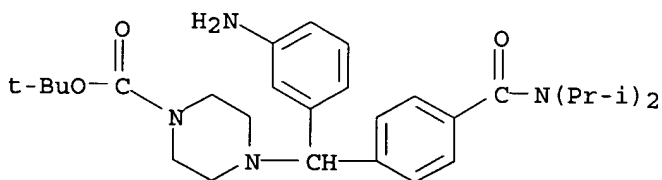
RN 477191-73-4 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[[4-[[bis(1-methylethyl)amino]carbonyl]phenyl][3-(3-nitrophenyl)methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 477191-75-6 CAPLUS

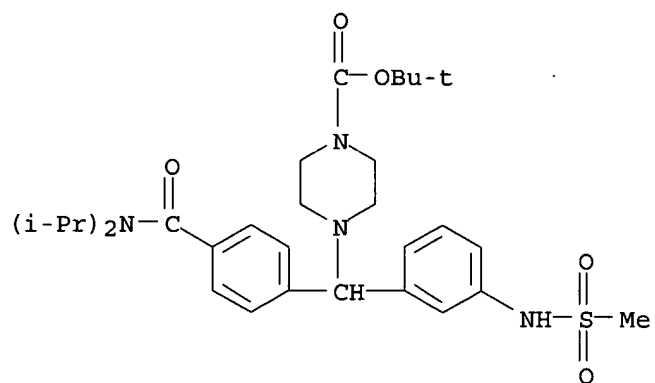
CN 1-Piperazinecarboxylic acid, 4-[(3-aminophenyl)[4-[[bis(1-methylethyl)amino]carbonyl]phenyl]methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 477191-76-7 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[[4-[[bis(1-methylethyl)amino]carbonyl]phenyl][3-[(methylsulfonyl)amino]phenyl]methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

10/076448

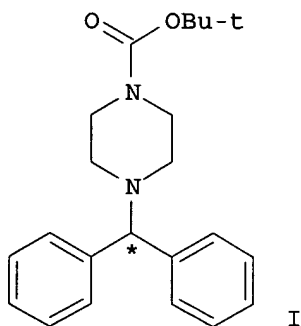


RE.CNT 3      THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/076448

L7 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 2002:671907 CAPLUS  
DN 137:201336  
TI A process for the preparation of an optically active 4-(tert-butoxycarbonyl) piperazine compound  
IN Kudo, Junko; Hirata, Norihiko; Yoshida, Tomoyasu  
PA Sumitomo Chemical Company, Limited, Japan  
SO Eur. Pat. Appl., 20 pp.  
CODEN: EPXXDW  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1236722	A1	20020904	EP 2002-251162	20020220
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2002249487	A2	20020906	JP 2001-46390	20010222
	US 2002128275	A1	20020912	US 2002-76448	20020219
PRAI	JP 2001-46390	A	20010222		
OS	MARPAT 137:201336				
GI					



Apps

AB Disclosed is a process for the prepn. of I [X = Cl, alkyl, alkoxy group; \* = asym. carbon atom] or a salt thereof. 1-[(4-Chlorophenyl)phenylmethyl]piperazine is converted to the Boc-deriv. (PhMe/water, Boc2O, NaOH, 35.degree.C). D-(+)-O,O'-dibenzoyltartaric acid is added to this intermediate (PhMe/MeOH, 30.degree.). The resulting mixt. is seeded and the tartrate salt of the (-)-piperazine is isolated (70.9% ee) by filtration. The ee of the salt is enriched by recrystn. with seeding. Neutralization of (-)-1-[(4-chlorophenyl)phenylmethyl]-4-(tert-butoxycarbonyl)piperazine D-(+)-O,O'-dibenzoyltartaric acid salt (98.2% ee) affords the free base of the (-)-isomer in 90% yield (98.4% ee). Deprotection is accomplished with EtOAc/HCl to afford (-)-1-[(4-chlorophenyl)phenylmethyl]piperazine dihydrochloride in quant. yield. The current process gives higher enantiomeric excess than prior art.

IT 454217-55-1P, 1-[(4-Chlorophenyl)phenylmethyl]-4-(tert-butoxycarbonyl)piperazine 454217-56-2P 454217-57-3P 454217-59-5P 454217-60-8P

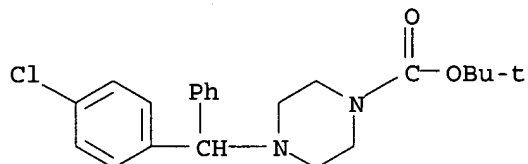
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; process for prepn. of optically active 4-(tert-butoxycarbonyl) piperazine compd.)

10/076448

RN 454217-55-1 CAPLUS

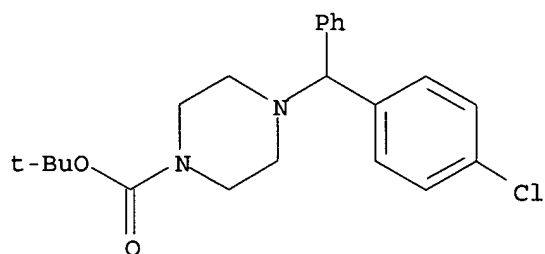
CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 454217-56-2 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, 1,1-dimethylethyl ester, (-) - (9CI) (CA INDEX NAME)

Rotation (-).



RN 454217-57-3 CAPLUS

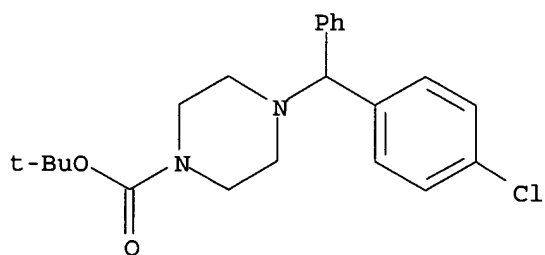
CN Butanedioic acid, 2,3-bis(benzoyloxy)-, (2S,3S)-, compd. with 1,1-dimethylethyl (-)-4-[(4-chlorophenyl)phenylmethyl]-1-piperazinecarboxylate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 454217-56-2

CMF C22 H27 Cl N2 O2

Rotation (-).



CM 2

CRN 17026-42-5

CMF C18 H14 O8

Absolute stereochemistry. Rotation (+).

O=C(O)[C@H](OC(=O)c1ccccc1)[C@@H](OC(=O)c1ccccc1)S(=O)(=O)C(=O)O

CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-,  
1,1-dimethylethyl ester, (+)- (9CI) (CA INDEX NAME)

CC(C)(C)OC(=O)N1CCN(C(C1)Cc2ccccc2)Cc3ccc(Cl)cc3

CN Butanedioic acid, 2,3-bis(benzoyloxy)-, (2R,3R)-, compd. with 1,1-dimethylethyl (+)-4-[(4-chlorophenyl)phenylmethyl]-1-piperazinecarboxylate (1:1) (9CI) (CA INDEX NAME)

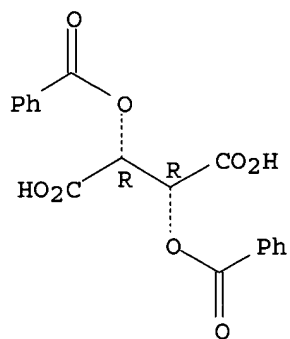
CRN 454217-59-5  
CMF C22 H27 Cl N2 O2

CCOC(=O)N1CCN(C(C1)c2ccccc2)c3ccc(Cl)cc3

CRN 2743-38-6  
CMF C18 H14 O8

10/076448

Absolute stereochemistry.



RE.CNT 1      THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/076448

L7 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 2002:534072 CAPLUS  
DN 137:93778  
TI Preparation of multibinding H1-histamine receptor antagonists  
IN Numerof, Robert P.; Ji, Yu-hua; Griffin, John H.  
PA Theravance, Inc., USA  
SO U.S., 77 pp.  
CODEN: USXXAM  
DT Patent  
LA English  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6420560	B1	20020716	US 1999-326627	19990607
PRAI	US 1999-326627		19990607		

OS MARPAT 137:93778

AB Novel multibinding compds., which are multimeric ligands, are disclosed as H1-histamine receptor antagonists. The compds. comprise 2-10 ligands, covalently connected via 1-20 linkers, with each ligand capable of binding to the H1 histamine receptor. Fourteen prophetic examples are given to illustrate the invention. Accordingly, the multibinding compds. and pharmaceutical compns. of this invention are useful in the treatment and prevention of allergic diseases such as rhinitis, urticaria, asthma, and anaphylaxis, and the like.

IT 441787-25-3P

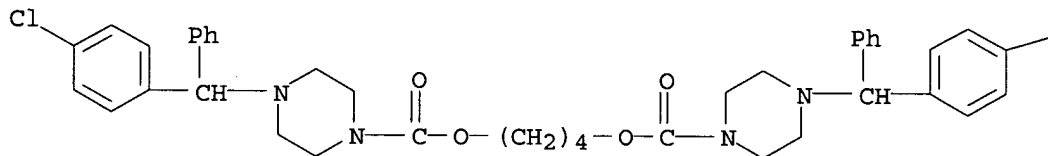
RL: PAC (Pharmacological activity); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of multibinding H1-histamine receptor antagonists contg. nitrogen heterocyclic ligands)

RN 441787-25-3 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, 1,4-butanediyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

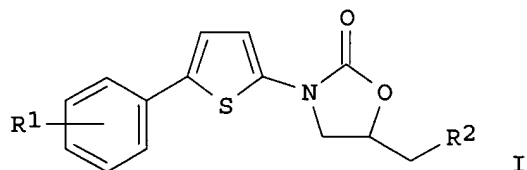
—Cl

RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/076448

L7 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 2002:83983 CAPLUS  
DN 136:151156  
TI Preparation of 3-(5-phenylthien-2-yl)oxazolidin-2-ones as TNF inhibitors  
IN Mueller, Ulrich; Handke, Gabriele; Fischer, Ruediger; Petesch, Nicole;  
Schmeck, Carsten; Kretschmer, Axel; Nielsch, Ulrich; Bremm, Klaus-Dieter;  
Zaiss, Siegfried  
PA Bayer A.-G., Germany  
SO Ger. Offen., 54 pp.  
CODEN: GWXXBX  
DT Patent  
LA German  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 10034625	A1	20020131	DE 2000-10034625	20000717
PRAI	DE 2000-10034625		20000717		
OS	MARPAT 136:151156				
GI					

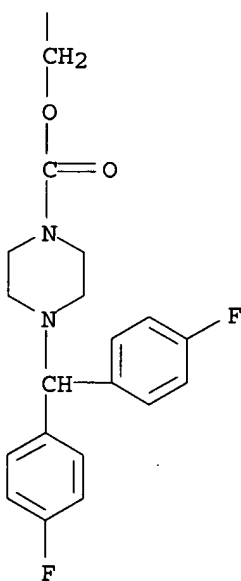
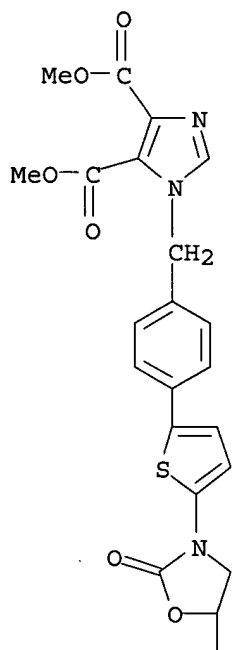


AB Title compds. [I; R1 = (substituted) (annelated) alkylheterocyclyl; R2 = amino (fused) OH], were prepd. Thus, 1-(4-[5-(1-hydroxymethyl-2-oxooxazolidin-3-yl)thien-2-yl]benzyl)-1H-imidazole-4,5-dicarboxylic acid di-Me ester was obtained in an yield of 97% by Mitsunobu reaction of 3-[5-(4-formylphenyl)thien-2-yl]-5-[dimethyl-(1,1-dimethylethyl)silyloxymethyl]oxazolidin-2-one (prepn. given) with 1H-imidazole-4,5-dicarboxylic acid di-Me ester. Several I tested by an enzyme-linked immuno sorbent assay (ELISA) gave 50% TNF-.alpha. biosynthesis inhibition with EC50 = 500-8,000 nM in human blood monocytes.

IT **392682-76-7P**  
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(prepn. of (phenylthienyl)oxazolidinones as TNF inhibitors)

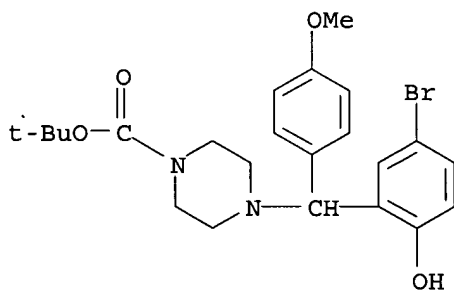
RN 392682-76-7 CAPLUS

CN 1H-Imidazole-4,5-dicarboxylic acid, 1-[[4-[5-[5-[[[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]carbonyl]oxy]methyl]-2-oxo-3-oxazolidinyl]-2-thienyl]phenyl]methyl]-, dimethyl ester (9CI) (CA INDEX NAME)



10/076448

L7 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 2001:85098 CAPLUS  
DN 134:295691  
TI One-step three-component reaction among organoboronic acids, amines, and salicylaldehydes  
AU Petasis, N. A.; Boral, S.  
CS Department of Chemistry and Loker Hydrocarbon Research Institute, University of Southern California, Los Angeles, CA, 90089-1661, USA  
SO Tetrahedron Letters (2001), 42(4), 539-542  
CODEN: TELEAY; ISSN: 0040-4039  
PB Elsevier Science Ltd.  
DT Journal  
LA English  
OS CASREACT 134:295691  
AB Alkenyl-, aryl-, and heteroarylboronic acids react with amines and salicylaldehydes in a single step to give novel amino phenols.  
IT 333999-37-4P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of amino phenols by three-component reaction of organoboronic acids, amines, and salicylaldehydes)  
RN 333999-37-4 CAPLUS  
CN 1-Piperazinecarboxylic acid, 4-[(5-bromo-2-hydroxyphenyl)(4-methoxyphenyl)methyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2003 ACS

AN 2000:653165 CAPLUS

DN 134:4912

TI New Diarylmethylpiperazines as Potent and Selective Nonpeptidic .delta. Opioid Receptor Agonists with Increased In Vitro Metabolic Stability

AU Plobeck, Niklas; Delorme, Daniel; Wei, Zhong-Yong; Yang, Hua; Zhou, Fei; Schwarz, Peter; Gawell, Lars; Gagnon, Helene; Pelcman, Benjamin; Schmidt, Ralf; Yue, Shi Yi; Walpole, Christopher; Brown, William; Zhou, Edward; Labarre, Maryse; Payza, Kemal; St-Onge, Stephane; Kamassah, Augustus; Morin, Pierre-Emmanuel; Projean, Denis; Ducharme, Julie; Roberts, Edward

CS Departments of Chemistry and Pharmacology, Astra Zeneca R&D Montreal, Saint-Laurent, QC, H4S 1Z9, Can.

SO Journal of Medicinal Chemistry (2000), 43(21), 3878-3894  
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

OS CASREACT 134:4912

AB Nonpeptide .delta. opioid agonists are analgesics with a potentially improved side-effect and abuse liability profile, compared to classical opioids. Andrews anal. of the NIH nonpeptide lead SNC-80 suggested the removal of substituents not predicted to contribute to binding. This approach led to a simplified lead, N,N-diethyl-4-[phenyl(1-piperazinyl)methyl]benzamide which retained potent binding affinity and selectivity to the human .delta. receptor ( $IC_{50} = 11 \text{ nM}$ ,  $\mu\text{M}/\text{.delta.} = 740$ ,  $\kappa\text{M}/\text{.delta.} > 900$ ) and potency as a full agonist ( $EC_{50} = 36 \text{ nM}$ ) but had a markedly reduced mol. wt., only one chiral center, and increased in vitro metabolic stability. From this lead, the key pharmacophore groups for .delta. receptor affinity and activation were more clearly defined by SAR and mutagenesis studies. Further structural modifications confirmed the importance of the N,N-diethylbenzamide group and the piperazine lower basic nitrogen for .delta. binding, in agreement with mutagenesis data. A no. of piperazine N-alkyl substituents were tolerated. In contrast, modifications of the Ph group led to the discovery of a series of diarylmethylpiperazines exemplified by N,N-diethyl-4-[1-piperazinyl(8-quinolinyl)methyl]benzamide which had an improved in vitro binding profile ( $IC_{50} = 0.5 \text{ nM}$ ,  $\mu\text{M}/\text{.delta.} = 1239$ ,  $EC_{50} = 3.6 \text{ nM}$ ) and increased in vitro metabolic stability compared to SNC-80.

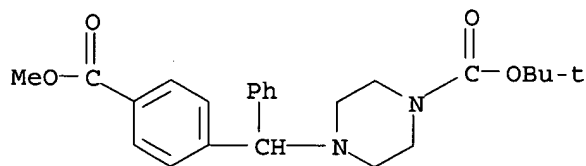
IT 193217-01-5P 193217-37-7P 308110-11-4P  
308110-12-5P

RE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(diarylmethylpiperazines as potent and selective nonpeptidic .delta. opioid receptor agonists with increased in vitro metabolic stability)

RN 193217-01-5 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[[4-(methoxycarbonyl)phenyl]phenylmethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

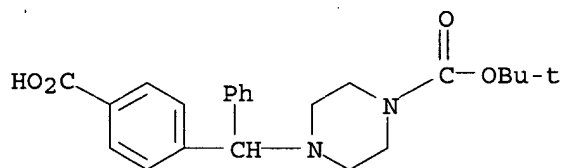


RN 193217-37-7 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[(4-carboxyphenyl)phenylmethyl]-,

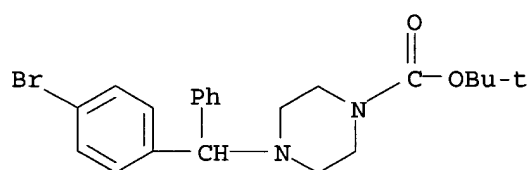
10/076448

1-(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



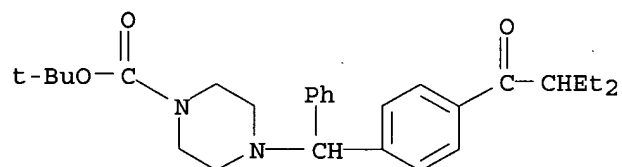
RN 308110-11-4 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[(4-bromophenyl)phenylmethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 308110-12-5 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[[4-(2-ethyl-1-oxobutyl)phenyl]phenylmethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



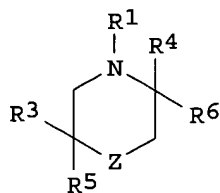
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

10/076448

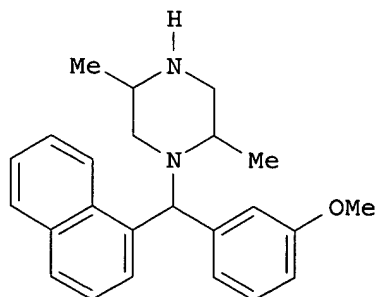
L7 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 1997:506552 CAPLUS  
DN 127:149159  
TI Preparation of N-diarylmethylpiperazines as analgesics  
IN Roberts, Edward; Plobeck, Niklas; Wahlestedt, Claes  
PA Astra Pharma Inc., Can.; Astra Aktiebolag (Publ); Roberts, Edward;  
Plobeck, Niklas; Wahlestedt, Claes  
SO PCT Int. Appl., 110 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

*SgA*

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9723466	A1	19970703	WO 1996-SE1635	19961211
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9610352	A	19970623	ZA 1996-10352	19961209
AU 9712162	A1	19970717	AU 1997-12162	19961211
AU 715547	B2	20000203		
CN 1209124	A	19990224	CN 1996-180102	19961211
EP 915855	A1	19990519	EP 1996-943426	19961211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9612204	A	19990713	BR 1996-12204	19961211
NZ 324887	A	20000128	NZ 1996-324887	19961211
JP 2000502679	T2	20000307	JP 1997-523557	19961211
SK 282743	B6	20021106	SK 1998-822	19961211
RU 2194702	C2	20021220	RU 1998-113786	19961211
TW 458971	B	20011011	TW 1996-85115800	19961220
US 6130222	A	20001010	US 1997-836830	19970424
NO 9802807	A	19980819	NO 1998-2807	19980618
PRAI SE 1995-4661	A	19951222		
WO 1996-SE1635	W	19961211		
OS MARPAT 127:149159				
GI				



I



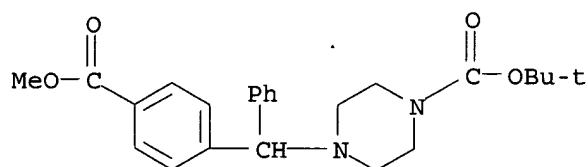
II

AB Title compds. [I; R1 = H, alkyl, (hetero)aryl, etc.; R3-R6 = groups cited for R1, amino(alkyl), carbamoyl(alkyl), etc.; Z = CHCR2R7R8 or NCR2R7R8; R2 = H, Me, OR1, CO2R1, CH2CO2R1; R7 = aminophenyl, acylphenyl, quinolyl, etc.; R8 = (hetero)aryl] were prepd. as analgesics (no data). Thus, 3-(MeO)C6H4Br was treated with BuLi and the product condensed with 1-naphthaldehyde to give, after chlorination and amination with trans-2,5-dimethylpiperazine, title compd. trans-II.

IT **193217-01-5P**  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (prepn. of N-diarylmethylpiperazines as analgesics)

RN 193217-01-5 CAPLUS

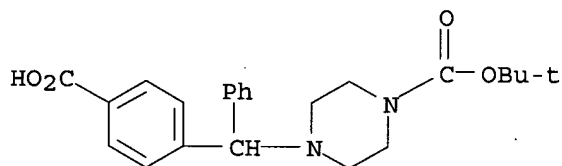
CN 1-Piperazinecarboxylic acid, 4-[[4-(methoxycarbonyl)phenyl]phenylmethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



IT **193217-37-7P**  
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
 (prepn. of N-diarylmethylpiperazines as analgesics)

RN 193217-37-7 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[(4-carboxyphenyl)phenylmethyl]-, 1-(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

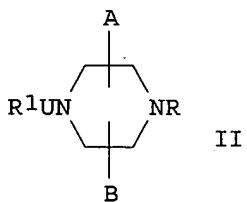
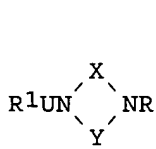


10/076448

L7 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 1997:499179 CAPLUS  
DN 127:176441  
TI Preparation of N-heterocyclylalkyl- or N-[(polycyclyl)-alkyl]-N'-  
substituted piperazines as insecticides.  
IN Silverman, Ian R.; Ali, Syed F.; Cohen, Daniel H.; Lyga, John W.; Simmons,  
Kirk A.; Cullen, Thomas G.  
PA FMC Corp., USA  
SO PCT Int. Appl., 59 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

*see Saw*

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9726252	A1	19970724	WO 1997-US804	19970115
	W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
	US 2007	H1	20011204	US 1997-780371	19970109
	AU 9715809	A1	19970811	AU 1997-15809	19970115
PRAI	US 1996-10237P	P	19960119		
	US 1997-780371	A	19970109		
	WO 1997-US804	W	19970115		
OS	MARPAT 127:176441				
GI					



AB Title compds. [I; A, B = alkyl; U = alkylene, alkenylene, CHZ; Z = H, alkyl, cycloalkyl, Ph; R = (substituted) Ph, dibenzocycloalkyl, etc.; R1 = (substituted) Ph, naphthyl, tetrazolylphenyl, benzothienyl, benzimidazolyl, indolyl, pyrrolyl, quinolinyl, etc.; X = (CH2)m; Y = (CH2)n; m = 2,3; n = 1-3], were prepd. Thus, reaction of N-[bis(4-trifluoromethylphenyl)methyl]piperazine and 4-(pyrid-2-yloxy)benzyl chloride in Me2SO contg. NaI and diisopropylethylamine gave N-[4-(pyrid-2-yloxy)phenylmethyl]-N'-[bis(4-trifluoromethylphenyl)methyl]piperazine. The latter at 50 micromolar in feed gave 100% inhibition of the growth of tobacco budworms.

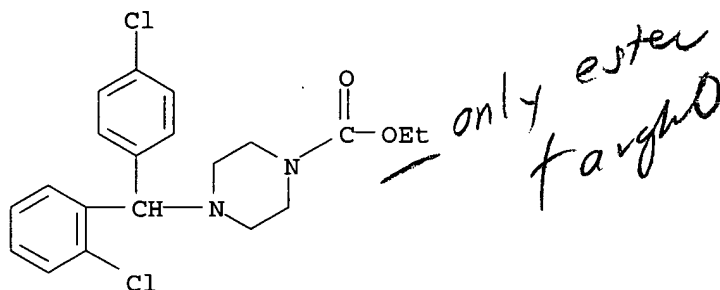
IT 194017-61-3P 194017-66-8P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(prepn. of N-heterocyclylalkyl- or N-[(polycyclyl)-alkyl]-N'-substituted piperazines as insecticides)

RN 194017-61-3 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[(2-chlorophenyl)(4-chlorophenyl)methyl]-,

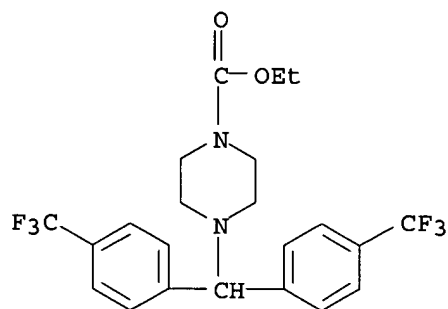
10/076448

ethyl ester (9CI) (CA INDEX NAME)



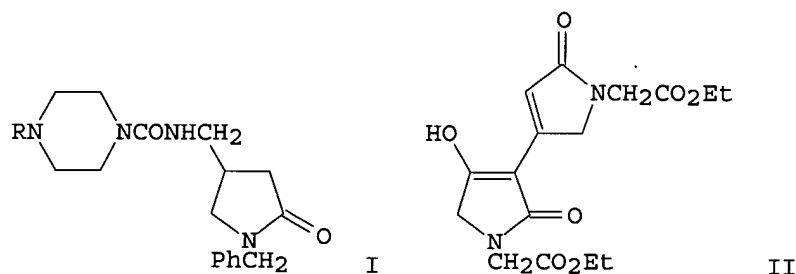
RN 194017-66-8 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[bis[4-(trifluoromethyl)phenyl]methyl]-, ethyl ester (9CI) (CA INDEX NAME)



10/076448

L7 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 1994:508424 CAPLUS  
DN 121:108424  
TI Potential nootropic agents: synthesis of some 1,4-disubstituted  
2-oxopyrrolidines and some related compounds  
AU Valenta, Vladimir; Urban, Jiri; Taimr, Jan; Polivka, Zdenek  
CS Res. Inst. Pharm. Biochem., Prague, 130 60, Czech Rep.  
SO Collection of Czechoslovak Chemical Communications (1994), 59(5), 1126-36  
CODEN: CCCCAK; ISSN: 0010-0765  
DT Journal  
LA English  
GI

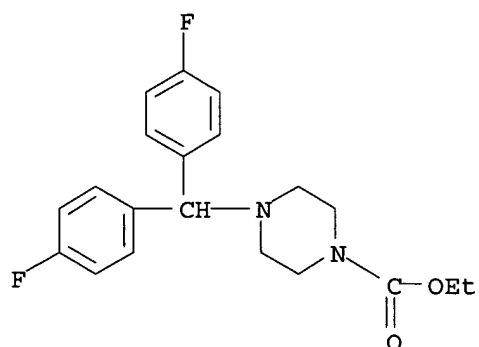


AB 4-(Aminomethyl)-1-benzyl-2-oxopyrrolidine was transformed by treatment with (4-benzhydrylpiperazin-1-yl)carbonyl chlorides and with (4-methylpiperazin-1-yl)carbonyl chloride to the carboxamides I (R = Me, Ph<sub>2</sub>CH, substituted benzhydryl). Heating of 1-(ethoxycarbonylmethyl)-2,4-dioxopyrrolidine in acetonitrile in the presence of water afforded II. Treatment with ammonia led to the diamide, while alk. hydrolysis of II gave the dicarboxylic acid. 4-(Aminomethyl)-1-(4-methylthiobenzyl)-2-oxopyrrolidine was prepd. by the reaction of 4-(methylthio)benzylamine with itaconic acid and the following sequence of reactions starting from the obtained carboxylic acid including esterification, redn. and treatment the obtained alc. with thionyl chloride, synthesis of phthalimido deriv. and hydrazinolysis. The compds. prepd. were tested for nootropic activity.

IT 156640-07-2P 156640-08-3P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(prepn. and reaction of, in prepn. of nootropic disubstituted oxopyrrolidines)

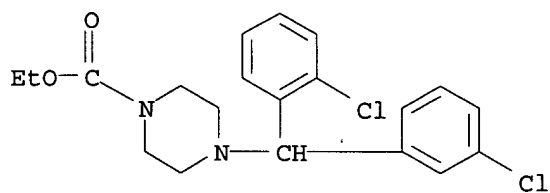
RN 156640-07-2 CAPLUS  
CN 1-Piperazinecarboxylic acid, 4-[bis(4-fluorophenyl)methyl]-, ethyl ester (9CI) (CA INDEX NAME)

10/076448

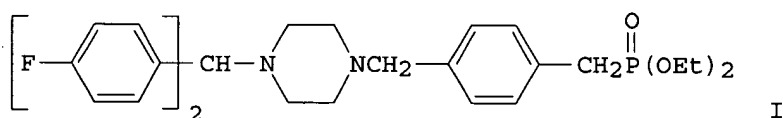


RN 156640-08-3 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[(2-chlorophenyl)(3-chlorophenyl)methyl]-, ethyl ester (9CI) (CA INDEX NAME)



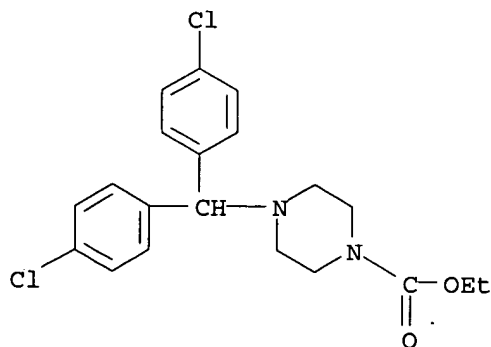
L7 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2003 ACS  
 AN 1994:270311 CAPLUS  
 DN 120:270311  
 TI Synthesis and pharmacological study of new calcium antagonists, analogs of cinnarizine and flunarizine  
 AU Younes, S.; Baziard-Mouysset, G.; de Saqui-Sannes, G.; Stigliani, J. L.; Payard, M.; Bonnafeous, R.; Tisne-Versailles, J.  
 CS Dep. Chim. Pharm., Fac. Pharm., Toulouse, F-31400, Fr.  
 SO European Journal of Medicinal Chemistry (1993), 28(12), 943-8  
 CODEN: EJMCA5; ISSN: 0223-5234  
 DT Journal  
 LA English  
 GI



AB Several phosphonic di-Et esters were prepd. and their Ca antagonistic activity evaluated in vitro. The di-Et phosphonate group was condensed on substituted [diphenylmethyl], [(2-benzofuranyl)phenylmethyl], [(4-diphenylmethyl-1-piperazinyl) methyl], [4-(4-diphenylmethyl-1-piperazinyl methyl) phenylmethyl], and [4-(3-phenyl-2-propenyl)-1-piperazinyl methyl] groups. Despite the presence of the di-Et phosphonate moiety and the benzhydrylpiperazinyl group, both present in potent Ca antagonist structures, only one of the 19 prepd. compds., i.e. I, exhibited a Ca antagonistic profile.

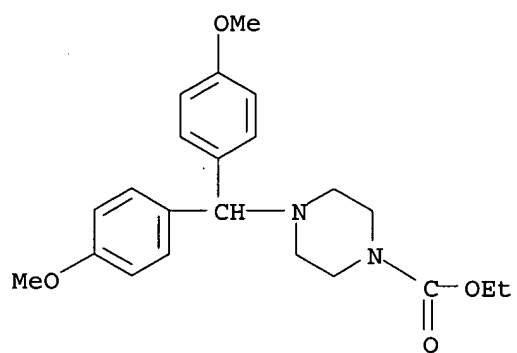
IT **154544-61-3P 154544-62-4P**  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. of, as intermediate for (piperazinylmethyl)benzyl phosphonate calcium antagonist)

RN 154544-61-3 CAPLUS  
 CN 1-Piperazinecarboxylic acid, 4-[bis(4-chlorophenyl)methyl]-, ethyl ester (9CI) (CA INDEX NAME)



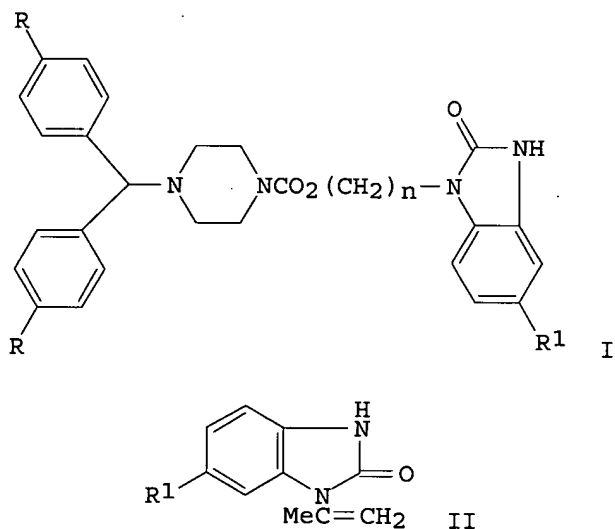
RN 154544-62-4 CAPLUS  
 CN 1-Piperazinecarboxylic acid, 4-[bis(4-methoxyphenyl)methyl]-, ethyl ester (9CI) (CA INDEX NAME)

10/076448



10/076448

L7 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 1989:439313 CAPLUS  
DN 111:39313  
TI Potential H1-antihistaminic drugs: synthesis of 4-[(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)alkoxycarbonyl]-1-(diphenylmethyl)piperazines by selective monoalkoxycarbonylation of .alpha.,.omega.-dichloroalkanes with phase-transfer catalysis  
AU Gomez-Parra, Vicente; Jimenez, Mercedes; Sanchez, Felix; Torres, Tomas  
CS Inst. Quim. Org., CSIC, Madrid, E-28006, Spain  
SO Liebigs Annalen der Chemie (1989), (6), 539-44  
CODEN: LACHDL; ISSN: 0170-2041  
DT Journal  
LA English  
OS CASREACT 111:39313  
GI

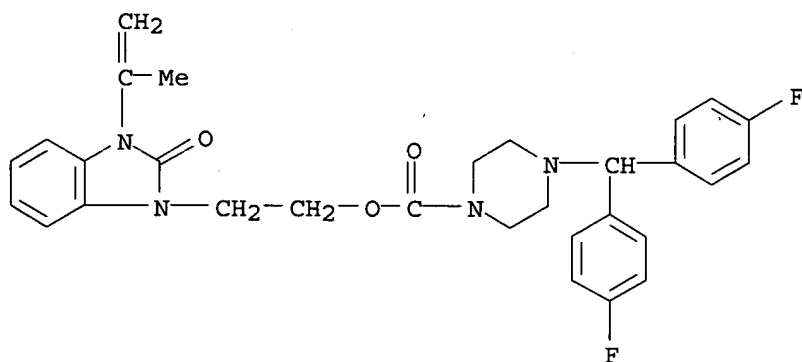


AB The title compds. I (R = H, F; R1 = H, Me, Cl; n = 2, 3, 4) were prepd. by phase transfer-catalyzed monoalkoxycarbonylation of .alpha.,.omega.-dichloroalkanes is described. I are related to oxatomide and are potential histamine-H1 antagonists. A study on the regioselective prepn. of substituted 1,3-dihydro-1-isoprenyl-2H-benzimidazol-2-ones II (R1 = Cl, Me) was also carried out.

IT 120311-79-7P 120311-83-3P 120311-87-7P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)  
(prepn. and hydrolysis of)

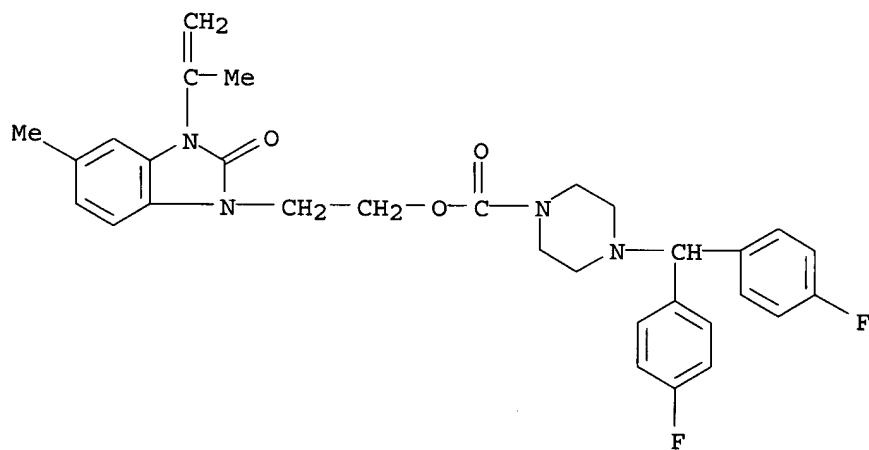
RN 120311-79-7 CAPLUS  
CN 1-Piperazinecarboxylic acid, 4-[bis(4-fluorophenyl)methyl]-,  
2-[2,3-dihydro-3-(1-methylethenyl)-2-oxo-1H-benzimidazol-1-yl]ethyl ester  
(9CI) (CA INDEX NAME)

10/076448



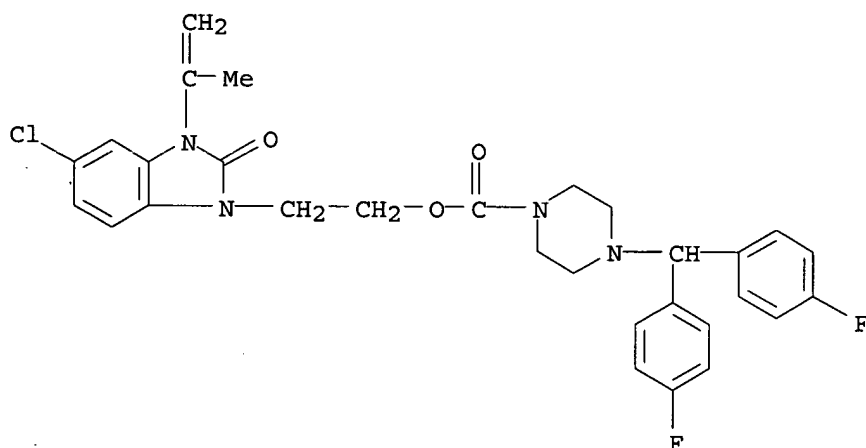
RN 120311-83-3 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[bis(4-fluorophenyl)methyl]-,  
2-[2,3-dihydro-5-methyl-3-(1-methylethenyl)-2-oxo-1H-benzimidazol-1-yl]ethyl ester (9CI) (CA INDEX NAME)



RN 120311-87-7 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[bis(4-fluorophenyl)methyl]-,  
2-[5-chloro-2,3-dihydro-3-(1-methylethenyl)-2-oxo-1H-benzimidazol-1-yl]ethyl ester (9CI) (CA INDEX NAME)



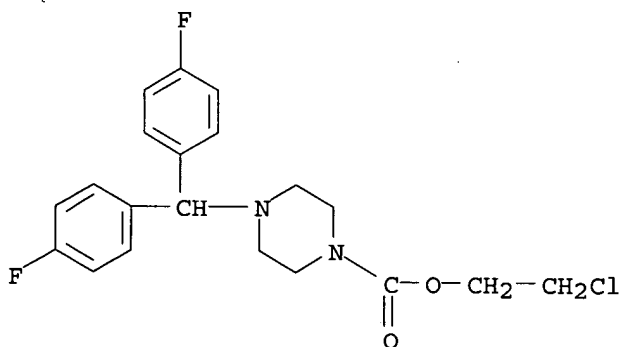
IT 120311-74-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. and reaction with chlorodihydro(methylethenyl)benzimidazolones)

RN 120311-74-2 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[bis(4-fluorophenyl)methyl]-, 2-chloroethyl ester (9CI) (CA INDEX NAME)



IT 120311-91-3P 120311-95-7P 120311-99-1P

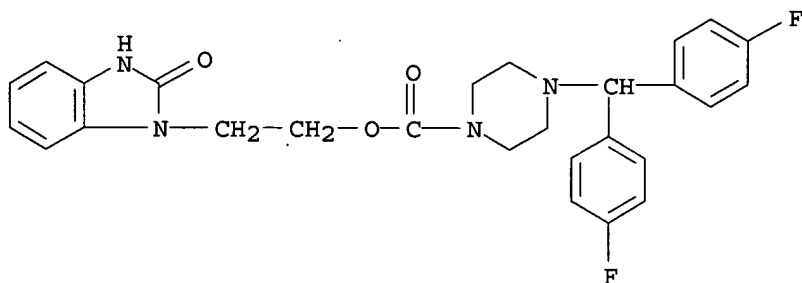
RL: SPN (Synthetic preparation); PREP (Preparation)

(prepn. of, as histamine-H1 antagonists)

RN 120311-91-3 CAPLUS

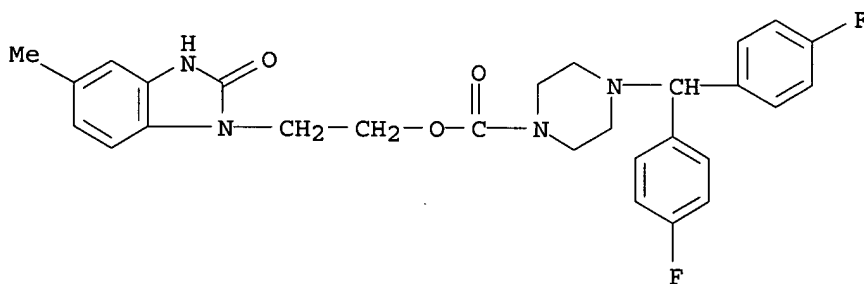
CN 1-Piperazinecarboxylic acid, 4-[bis(4-fluorophenyl)methyl]-, 2-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)ethyl ester (9CI) (CA INDEX NAME)

10/076448



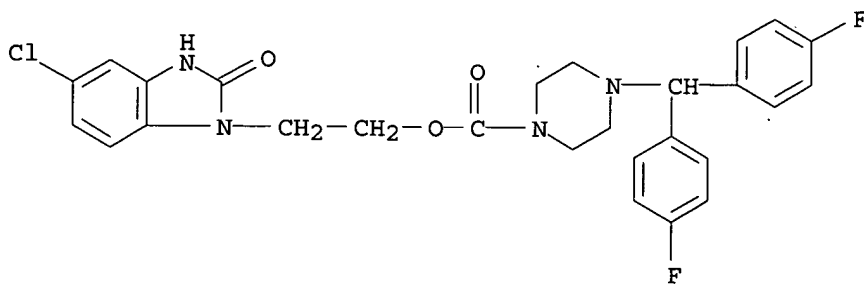
RN 120311-95-7 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[bis(4-fluorophenyl)methyl]-,  
2-(2,3-dihydro-5-methyl-2-oxo-1H-benzimidazol-1-yl)ethyl ester (9CI) (CA  
INDEX NAME)



RN 120311-99-1 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[bis(4-fluorophenyl)methyl]-,  
2-(5-chloro-2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)ethyl ester (9CI) (CA  
INDEX NAME)

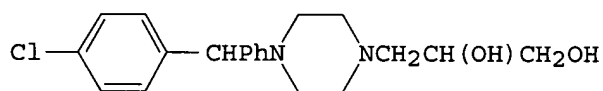


10/076448

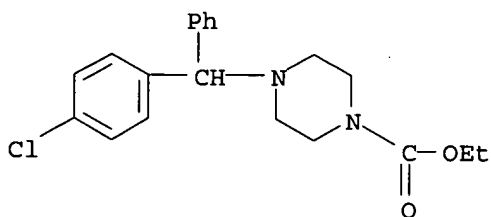
L7 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 1982:52334 CAPLUS  
DN 96:52334  
TI 1-(4-Chlorobenzhydryl)-4-(2,3-bishydroxypropyl)-piperazine, its use as an  
antitussive agent, an antihistamine, a sedative, an analgesic and an  
antiinflammatory agent as well as pharmaceutical preparations containing  
it  
PA Selvi e C. S.p.A., Italy  
SO Belg., 18 pp.  
CODEN: BEXXAL  
DT Patent  
LA Dutch  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	BE 888811	A2	19810828	BE 1981-59160	19810515
	DE 3118162	A1	19820218	DE 1981-3118162	19810507
	DE 3118162	C2	19840726		
	FR 2482965	A1	19811127	FR 1981-9273	19810508
	FR 2482965	B1	19841123		
	NL 8102361	A	19811216	NL 1981-2361	19810513
	GB 2076403	A	19811202	GB 1981-15827	19810522
	ES 502429	A1	19820401	ES 1981-502429	19810522
	JP 57031678	A2	19820220	JP 1981-78562	19810523
	JP 61035189	B4	19860812		
PRAI	IT 1980-22283		19800523		

GI



AB The title compd. was prepd. and found superior to codeine in title  
activity. Thus, Et 1-piperazinecarboxylate was alkylated with  
4-ClC6H4CHPhBr, decarboxylated, and treated with glycidol to give I.  
IT **80476-89-7P**  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(prepn. and decarboxylation of)  
RN 80476-89-7 CAPLUS  
CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, ethyl  
ester (9CI) (CA INDEX NAME)



L7 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2003 ACS

AN 1960:62825 CAPLUS

DN 54:62825

OREF 54:12169a-h

TI Piperazine derivatives

IN Morren, H. G.

DT Patent

LA Unavailable

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	BE 549420		19570110	BE	
	DE 1062248			DE	
AB	<p>1-[2-(o-Chlorobenzhydryloxy)ethyl]-4-[2-(2-hydroxyethoxy)ethyl]piperazine, b0.1 230.degree., was prepd. in 80% yield by heating at 100.degree. for 15 hrs. a stirred mixt. of 0.1 mole 1-[2-(o-chlorobenzhydryloxy)ethyl]piperazine (I), 0.11 mole Et3N, and 0.1 mole 2-(2-chloroethoxy)ethanol in 100 cc. toluene; di-HCl salt m. 150.degree.. With A = 2-(o-chlorobenzhydryloxy)ethyl group, the following derivs. were prepd.:</p> <p>1-A-substituted-4-isopropylpiperazine, b0.04 184-6.degree. (di-HCl salt m. 203.degree.), in 88% yield by refluxing 1 mole 1-isopropylpiperazine, 1.1 moles Et3N, and 1 mole 2-chloroethyl o-chlorobenzhydryl ether (II) 18 hrs. in 600 cc. xylene. 1-A-Substituted-(m-methylbenzyl)piperazine, b0.1 240.degree. (di-HCl salt m. 224-6.degree.), in 50% yield, by heating under N at 160.degree. for 3 hrs., 0.1 mole 1-(m-methylbenzyl)-4-(2-hydroxyethyl)piperazine and 0.1 mole o-chlorobenzhydryl chloride.</p> <p>1-A-Substituted-4-[2-(p-tert-butylbenzyloxy)ethyl]piperazine, b0.1 275.degree., in 50% yield from o-chlorobenzhydrol and 1-[2-(p-tert-butylbenzyloxy)ethyl]-4-(2-chloroethyl)piperazine at 160.degree. under N for 3 hrs. 1-A-Substituted-4-acetyl piperazine (III), b0.02 220.degree. in 94% yield from I and AcCl in presence of Et3N toluene soln. and similarly 1-A-substituted-4-(o-chlorobenzoyl)piperazine, b0.1 255.degree. (di-HCl salt m. 210-12.degree.). 1-A-Substituted-4-ethylpiperazine, b0.03 178-80.degree. (di-HCl salt m. 186-8.degree.), in 88% yield, by refluxing for 18 hrs. under N, 0.1 mole III, and 0.15 mole LiAlH4 suspended in Et2O. 1-A-Substituted-4-methylpiperazine, b0.1 185-90.degree. (di-HCl salt m. 200.degree.), in 95% yield, by treating 0.1 mole I with a soln. of 24 cc. 40% aq. HCOH in 100 cc. EtOH, and redn. in an autoclave at 60.degree. for 3 hrs. under 50 kg. H in the presence of Raney Ni. 1-A-Substituted-4-butylpiperazine b0.1 210.degree. (di-HCl salt m. 200-3.degree.). 1-A-Substituted-4-isobutylpiperazine b0.02 188-90.degree.. 1-A-Substituted-4-(2-hydroxyethyl)piperazine b0.1 230.degree.; di-HCl salt m. 150.degree.. 1-A-Substituted-4-(2,3-dihydroxypropyl)piperazine decompd. on distn.; di-HCl salt m. 147-50.degree.. 1-A-Substituted-4-cyclohexylpiperazine b0.05 235-40.degree.; di-HCl salt m. 230-3.degree.. 1-A-Substituted-4-(3-methylcyclohexyl)piperazine b0.01 230-2.degree.; di-HCl salt m. 214-15.degree.. 1 A-Substituted-4-benzylpiperazine b0.1 230-5.degree.; di-HCl salt m. 210.degree.. 1-A-Substituted-4-(o-chlorobenzyl)piperazine b0.1 240-1.degree.; di-HCl salt m. 208-9.degree.. 1-A-Substituted-4-(o-methylbenzyl)piperazine b0.005 235.degree.. 1-A-Substituted-4-(p-tert-butylbenzyl)piperazine b0.1 245-50.degree.; di-HCl salt m. 212-14.degree.. 1-[2-(o-Methylbenzhydryloxy)ethyl]-4-(o-methoxybenzyl)piperazine b0.01 234-6.degree. and the corresponding 4-isopropyl-, 4-(o-methylbenzyl)-, and 4-(m-methylbenzyl)piperazines resp. b0.002 175.degree., b0.01 218-20.degree., and b0.015 224.degree.. II, b0.1 143.degree., was obtained in 90% yield from 2-chloroethanol and chlorobenzhydrol in presence of H2SO4. Similarly prepd. was 2-chloroethyl o-methylbenzhydryl ether, b0.04 137.degree.. I, b0.007 185.degree. (di-HCl salt m. 105-7.degree.), was prepd. in 85% yield by refluxing 4 hrs. anhyd. piperazine (3.5 moles) and 1 mole II in 100 cc. xylene.</p>				

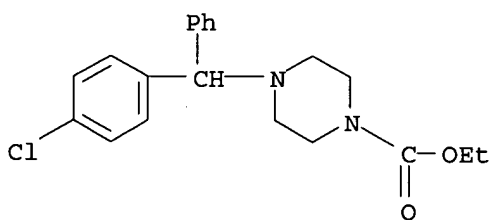
10/076448

1-Cyclohexylpiperazine, b12 129-31.degree., was prepd. in 30% yield by refluxing for several hrs. cyclohexyl bromide and excess anhyd. piperazine in xylene. 1-[2-(o-Methylbenzhydryloxy)ethyl]piperazine, b0.005 168-70.degree., 1-(3-methylcyclohexyl)piperazine, b11 132-4.degree., and 1-(o-methylbenzyl)piperazine, b0.1 88.degree., were similarly prepd. 1-(2,3-Dihydroxypropyl)piperazine, b0.1 146.degree., m. 70.degree., was obtained in 40% yield by stirring below 30.degree. for several hrs., 1 mole epoxypropanol and 2 moles piperazine hexahydrate in 750 cc. H2O.

IT 80476-89-7, 1-Piperazinecarboxylic acid, 4-(p-chloro-.alpha.-phenylbenzyl)-, ethyl ester  
(prepn. of)

RN 80476-89-7 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, ethyl ester (9CI) (CA INDEX NAME)



L7 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2003 ACS

AN 1959:122232 CAPLUS

DN 53:122232

OREF 53:21986f-i,21987a-g

TI Unsymmetrically substituted piperazines. XII. Benzhydrylpiperazines and related compounds with spasmolytic and antifibrillatory action

AU Ide, Walter S.; Lorz, Emil; Phillips, Arthur P.; Russell, Peter B.; Baltzly, Richard; Blumfeld, Robert

CS Wellcome Research Labs., Tuckahoe, NY

SO Journal of Organic Chemistry (1959), 24, 459-63

CODEN: JOCEAH; ISSN: 0022-3263

DT Journal

LA Unavailable

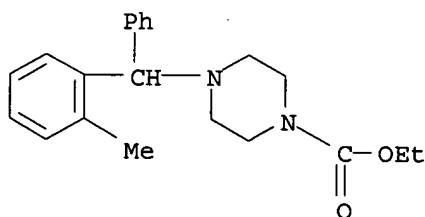
AB cf. C.A. 50, 4975b; 53, 11394h. In a study of compds. showing activity against artificial fibrillation, a no. of .omicron.-substituted benzhydrylpiperazines and related benzhydrylamines were prepd. The compds. were isolated, in general, by previously described techniques. The choice of mono or dihydrochlorides for the piperazines of the 1st series was largely a matter of convenience. A considerable no. of the mono-HCl salts of benzhydrylpiperazines could be crystd. from H<sub>2</sub>O and solns. have pH 5-5.5. The di-HCl salts are more readily crystd. from alc.-Et<sub>2</sub>O than the HCl salts. The following RN(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>NR' were prepd. (R, R', salt, and m.p. of salt given): PhCH(CH<sub>2</sub>)<sub>3</sub>Me, Me, di-HCl, 248.degree. (decompn.); PhCH(CH<sub>2</sub>)<sub>4</sub>Me, Me, di-HCl, 252.degree. (MeI deriv. m. 119.degree.); PhCHC<sub>6</sub>H<sub>11</sub>, Et (I), HCl, 266.degree.; Ph<sub>2</sub>CH, CHMe<sub>2</sub>, di-HCl, 218.degree.; MeO<sub>2</sub>CCH<sub>2</sub>CH<sub>2</sub>, Ph<sub>2</sub>CH, di-HCl, 190-1.degree.; p-H<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CO, Me, HCl, 238.degree.; p-H<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CO, PhCH<sub>2</sub>, di-HCl.2H<sub>2</sub>O, foams above 100.degree. unmelted at 250.degree.; p-H<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CO, Ph<sub>2</sub>CH, di-HCl.2H<sub>2</sub>O, foams above 100.degree. unmelted at 250.degree.; .omicron.-MeC<sub>6</sub>H<sub>4</sub>CHPh, CO<sub>2</sub>Et, HCl, 206.degree.; .omicron.-MeC<sub>6</sub>H<sub>4</sub>CHPh, H, HCl, 246.degree.; m-MeC<sub>6</sub>H<sub>4</sub>CHPh, CHMe<sub>2</sub>, di-HCl, 226.degree.; .omicron.-EtC<sub>6</sub>H<sub>4</sub>CHPh, Me, di-HCl, 223-5.degree.; .omicron.-ClC<sub>6</sub>H<sub>4</sub>CHPh, CHMe<sub>2</sub>, HCl, 272.degree.; (.omicron.-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CH, Me, di-HCl, 235.degree.; (p-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CH Me (II), HCl, 244-6.degree.; (.omicron.-EtC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CH, Me, di-HCl, 218.degree.; Ph<sub>3</sub>C, Me, HCl, 186-91.degree.. The following PhCHNR<sub>2</sub>' were obtained (R, NR<sub>2</sub>', salt, m.p. of salt given): .omicron.-ClC<sub>6</sub>H<sub>4</sub>, NHMe, HCl, 214.5-15.0.degree.; .omicron.-ClC<sub>6</sub>H<sub>4</sub>, NMe<sub>2</sub>, HCl, 233-3.5.degree.; ogr.-ClC<sub>6</sub>H<sub>4</sub>, NC<sub>5</sub>H<sub>10</sub>, HCl, 240-1.degree.; .omicron.-MeC<sub>6</sub>H<sub>4</sub>, NC<sub>5</sub>H<sub>10</sub>, HCl, 265-6.degree.; .omicron.-MeC<sub>6</sub>H<sub>4</sub>, NC<sub>4</sub>H<sub>8</sub>O, HCl, 256.degree. (decompn.); .omicron.-ClC<sub>6</sub>H<sub>4</sub>, NH(CH<sub>2</sub>)<sub>2</sub>NMe<sub>2</sub>, di-HCl, 183-5.degree.; .omicron.-MeC<sub>6</sub>H<sub>4</sub>, NH(CH<sub>2</sub>)<sub>2</sub>NMe<sub>2</sub>, di-HCl, 199-200.degree.; Ph, NH(CH<sub>2</sub>)<sub>2</sub>NMe<sub>2</sub>, di-HCl, 206-7.degree.; Ph, NH(CH<sub>2</sub>)<sub>2</sub>NC<sub>4</sub>H<sub>8</sub>O, di-HCl, 243-4.degree.. The following PhCHRN(CH<sub>2</sub>)<sub>2</sub>NR'R<sub>2</sub>X were obtained (R, R', R<sub>2</sub>, X, and m.p. given): Ph, Me, C<sub>7</sub>H<sub>15</sub> Br, 183.degree.; p-ClC<sub>6</sub>H<sub>4</sub>, Me, C<sub>7</sub>H<sub>15</sub>, BrCl, 198.degree.; p-ClC<sub>6</sub>H<sub>4</sub>, Me, C<sub>12</sub>H<sub>25</sub>, BrCl, 156.degree.; C<sub>6</sub>H<sub>11</sub>, Me, Me, iodide, 214-15.degree.; C<sub>6</sub>H<sub>11</sub>, Me, Et, iodide, 173-4.degree.; C<sub>6</sub>H<sub>11</sub>, Me, C<sub>3</sub>H<sub>7</sub>, iodide, 182.degree.; C<sub>6</sub>H<sub>11</sub>, Me, iso-Pr, iodide, 194.degree.; C<sub>6</sub>H<sub>11</sub>, Me, Bu, iodide, 108-10.degree.; C<sub>6</sub>H<sub>11</sub>, Et, Et, iodide (III), 195.degree.; C<sub>6</sub>H<sub>11</sub>, Et, iso-Pr, iodide, 216.degree.. Hexahydrobenzhydrol (19.1 g.) in 100 cc. PhMe refluxed 1 hr. with 10 cc. SOCl<sub>2</sub>, left overnight, the volatiles removed, and the residual oil distd. at 1 mm. gave 16 g. hexahydrobenzhydryl chloride (IV), b. 99.5-102.degree.. IV contained no significant amt. of unsatd. hydrocarbon. IV (8.3 g.) refluxed 96 hrs. with 9.1 g. N-ethylpiperazine, the mixt. partitioned between Et<sub>2</sub>O and H<sub>2</sub>O, the Et<sub>2</sub>O layer evapd. and shaken with N HCl, and the base liberated gave I. I (1.6 g.) in 10 cc. Me<sub>2</sub>CO left 1 day with 2 g. EtI gave 1.3 g. III. IV (10 g.) refluxed 23.5 hrs. with 20 g. N-methylpiperazine in 100 cc. MeCN, refrigerated, and sepd. gave 8.4 g. II, m. 244-6.degree. (decompn.) (abs. alc.). Pyrrolidine (10 g.) refluxed 1 hr. with 12.5 g. Ph<sub>2</sub>CHCOCl in 50 cc. Me<sub>2</sub>CO gave N-diphenylacetylpyrrolidine (V), m. 162-3.degree.

(Et<sub>2</sub>O-MeOH). V (7.9 g.) refluxed 5 hrs. with 1.5 g. LiAlH<sub>4</sub> in 200 cc. Et<sub>2</sub>O, 5 cc. H<sub>2</sub>O added slowly, the Et<sub>2</sub>O ext. washed with dil. HCl, and the base liberated from the aq. layer gave N-(.alpha.,.alpha.-diphenylethyl)pyrrolidine, m. 174-5.degree. (Me<sub>2</sub>CO-Et<sub>2</sub>O). N-Diphenylacetyl-N'-methylpiperazine (8.8 g.) reduced as above with 2.5 g. LiAlH<sub>4</sub> gave N-diphenylethyl-N'-methylpiperazine; di-HCl salt m. 256-7.degree. (decompn.). Diphenyl-4-pyridylcarbinol (13 g.) in 150 cc. MeOH refluxed 22 hrs. with 7 cc. MeI gave .alpha.,.alpha.-diphenylpyridine-4-methanol methiodide, m. 234-5.degree. (MeOH-Et<sub>2</sub>O). .alpha.,.alpha.-Diphenylpiperidine-4-methanol (14 g.) with 20 cc. Me acrylate in 25 cc. C<sub>6</sub>H<sub>6</sub> kept 24 hrs. at 45-50.degree., refluxed 5 hrs., and evapd. in vacuo gave .alpha.,.alpha.-diphenyl-1-(carbomethoxyethyl)piperidine-4-methanol, m. 93-4.degree. (C<sub>6</sub>H<sub>6</sub>hexane). Methylation of the secondary base with excess MeI and alkali gave .alpha.,.alpha.-diphenyl-1-methylpiperidine-4-methanol-MeI, m. 219-20.degree. (Me<sub>2</sub>CO then alc.), .omicron.-MeC<sub>6</sub>H<sub>4</sub>MgBr (from 3.7 g. Mg and 28 g. .omicron.-MeC<sub>6</sub>H<sub>4</sub>Br) treated during 15 min. with 8 g. Me N-methylisonipecotate, left 2 hrs. at room temp., and refluxed 1 hr. gave after treatment with HCl gas 15-17 g. 1-methyl-4-(.omicron.-methylbenzoyl)piperidine (VI), m. 183-5.degree. (alc.-Et<sub>2</sub>O). Examn. of the material in the mother liquors gave 2 g. .alpha.,.alpha.-di(.omicron.-tolyl)-1-methylpiperidine-4-methanol (VII), m. 300-2.degree.. From the mother liquors of the above carbinol more material was obtained, m. 158.degree., which had the compn. of a ketone-HCl, possibly isomeric with VI or a dimorphism effect. VII was recovered after refluxing 2 hrs. with an equal vol. of AcOH or concd. HCl. With concd. H<sub>2</sub>SO<sub>4</sub> on the steam bath VII suffered extensive decompn. Benzhydryl chloride (5 g.) and 7.2 g. N-methyl-N'-(hydroxyethyl)piperazine in a little C<sub>6</sub>H<sub>6</sub> was warmed 3 days on the steam bath, the mixt. partitioned between Et<sub>2</sub>O and H<sub>2</sub>O, and the base in the Et<sub>2</sub>O layer converted into the HCl salt, m. 200.degree.. Treatment of an aq. soln. of the salt with alkali and excess MeI in Et<sub>2</sub>O gave N-benzhydryloxyethyl-N',N'-dimethylpiperazinium iodide, m. 182-5.degree. (alc. Et<sub>2</sub>O).

IT 112350-85-3, 1-Piperazinecarboxylic acid, 4-(o-methyl-.alpha.-phenylbenzyl)-, ethyl ester, hydrochloride  
(prepn. of)

RN 112350-85-3 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-(o-methyl-.alpha.-phenylbenzyl)-, ethyl ester, hydrochloride (6CI) (CA INDEX NAME)



● HCl

L7 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2003 ACS  
 AN 1959:40048 CAPLUS  
 DN 53:40048  
 OREF 53:7215f-i,7216a-c  
 TI Piperazine derivatives  
 IN Weston, Arthur W.; Hamlin, Kenneth E., Jr.  
 PA Abbott Laboratories  
 DT Patent  
 LA Unavailable  
 FAN.CNT 1

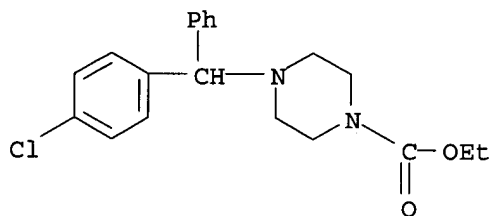
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2861072		19581118	US	
GI	For diagram(s), see printed CA Issue.				
AB	<p>R2R3R4CN.CH2.CH2.NR1.CH2.CH2 (I) were prepd., some of which are useful in combating the symptoms of histamine activity while others show antispasmodic activity. p-ClC6H4CHPhCl (11.9 g.), 5.0 g. N-methylpiperazine, and 5.3 g. Na2CO3 in 75 cc. anhyd. xylene refluxed and stirred 60 hrs., the xylene layer extd. several times with dil. HCl, the exts. combined, made alk. with NaOH, extd. with Et2O, the exts. combined, dried, and treated with gaseous HCl gave I (R1 = Me, R2 = H, R3 = Ph, R4 = p-ClC6H4) (II). 2HCl, m. 221.degree. (abs. EtOH-Et2O) [II.HCl, m. 223-4.degree. (abs. EtOH.)]. The following I were similarly prepd. [R1, R2, R3, R3, m.p. (or b.p.), and m.p. of di-HCl salt (or other deriv. given)]: Me, H, Ph, p-Br C6H4, b0.5 161-71.degree., 249-50.degree.; Me, H, Ph, Ph, 105-8.degree., 258-60.degree.; Me, H, Ph, p-MeOC6H4, b0.7 168-9.degree., 194-5.degree.; Me, H, p-ClC6H4, p-ClC6H4, -, 245-6.degree.; HOCH2CH2, H, Ph, Ph, -, 229.degree.; Et, H, Ph, Ph, -, 241.degree. (decompn.); Me2NCH2CH2, H, Ph, Ph, b0.7 158-62.degree., 255-7.degree. (decompn.); Me, H, Ph, p-IC6H4, b0.5 181.degree., 260-1.degree. (mono-HCl salt); H, H, Ph, Ph, 70-2.degree. (b1 183-90.degree.), 195.degree. (decompn.) (d-tartaric acid salt); Me, H, Ph, 2-pyridyl, 95-7.degree., -, Me, H, Ph, p-FC6H4, b0.6 140-1.degree., 230-1.degree. (mono-HCl salt); Me, H, Ph, p-MeC6H4, b1 159-60.degree., 228-9.degree. (mono-HCl salt); Me, H, p-ClC6H4, cyclohexyl, -, 278-9.degree. (decompn.); Et, H, Ph, p-ClC6H4, -, 227.5-8.0.degree.; Me, H, Ph, .omicron.-ClC6H4, b2 179-80.degree., 272-3.degree. (mono-HCl salt); Me, H, Ph, 2-thienyl, -, 202.degree. (decompn.); Bu, H, Ph, Ph, -, 248.degree. (decompn.); Bu, H, Ph, p-ClC6H4, -, 253.5-5.0.degree. (di-HBr salt); Me, H, Ph, m-ClC6H4, b1.5 177.degree., 249-50.degree. (mono-HCl salt); HOCH2, H, Ph, Ph, -, 189-90.degree.; Me, H, p-ClC6H4, 2-thienyl, -, 216.degree. (decompn.) (dioxalate); HO(CH2)4, H, Ph, p-ClC6H4, -, 211-12.degree. (decompn.); Me, Me, Ph, Ph, b0.7 162-5.degree., 203-5.degree. (contg. 1 H2O); H2NC(:NH), H, Ph, Ph, -, 294-5.degree. (sulfate); EtO2C, H, Ph, p-ClC6H4, -, -, EtO2C, H, Ph, Ph, 114.degree., -. Other compds. reported were: II, b0.1 150-2.degree.; II.MeI, m. 119-20.degree. (decompn.); HO(CH2)4N.CH2.CH2.N(CO2Et).CH2.CH2, b0.4 168.degree. (mono-HCl salt, m. 118-19.degree.); p-FC6H4CHPhCl, b1, 125-7.degree.; p-IC6H4CHPhCl, b0.6 148-9.degree.; .alpha.-(2-pyridyl)benzyl chloride, b0.3 126-31.degree.; .alpha.-cyclohexyl-p-chlorobenzyl chloride, b1.0 134-6.degree.; .alpha.-(2-thienyl)-p-chlorobenzyl chloride, unstable oil; p-ClC8H4ChPhN(CH2CH2Cl)2 HCl salt, m. 135-7.degree.; p-ClC6H4CHPhN(CH2CH2OH)2, b0.1 197-207.degree.; .alpha.-cyclohexyl-p-chlorophenylmethanol, b0.7 122-5.degree. m. 70-1.degree.; .alpha.-(2-thienyl)-p-chlorobenzyl alc., b0.3 157-8.degree., m. 58.5-60.0.degree.; Ph2CMeNH2, b4 140-2.degree. (di-HCl salt, m. 245-6.degree.); BuN.CH2.CH2. NH.CH2.CH2, b. 192-5.degree.; HO(CH2)4N.CH2.CH2.NH.CH2. CH2, b6 142.degree.; p-ClC6H4CHPhN.CH2.CH2.O.CH2.CH2, b0.3 162-5.degree..</p>				
IT	80476-89-7, 1-Piperazinecarboxylic acid, 4-(p-chloro-.alpha.-				

10/076448

phenylbenzyl)-, ethyl ester  
(prepn. of)

RN 80476-89-7 CAPLUS

CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, ethyl  
ester (9CI) (CA INDEX NAME)



L7 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2003 ACS

AN 1958:88366 CAPLUS

DN 52:88366

OREF 52:15598e-i,15599a-c

TI Benzhydryl carbalkoxy piperazines

IN Weston, Arthur W.; Hamlin, Kenneth E.

PA Abbott Laboratories

DT Patent

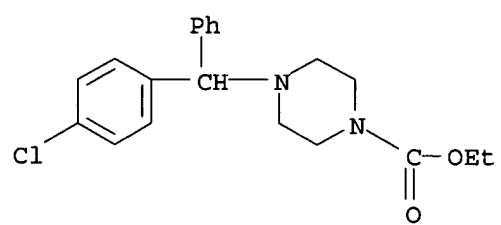
LA Unavailable

FAN.CNT 1

Sam

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2819269		19580107	US	
AB	<p>N-Benzhydryl-N1'-carbalkoxypiperazines of the formula  <math>R_2R_3R_4CN.CH_2.CH_2.NR_1.CH_2.CH_2</math>, where R1 is a 1-4 C atom carbalkoxy group, R2 is H or 1-4 C atom alkyl, R3 is phenyl or halophenyl and R4 is phenyl, halophenyl, pyridyl, thienyl or cyclohexyl, are prepd. by treating a benzhydryl halide with an N-carbalkoxypiperazine. N-Carbethoxypiperazine (I) (29.8 g.), 46.5 g. benzhydryl bromide, 21.2 g. Na<sub>2</sub>CO<sub>3</sub>, and 125 cc. dry xylene are refluxed 4 hrs. to yield N-benzhydryl-N'-carbethoxypiperazine (II), m. 114.degree.. II refluxed with concd. HCl or KOH yields N-benzhydrylpiperazine (III); e.g., 14 g. II and 56 g. KOH are refluxed 22 hrs. in 250 cc. 95% EtOH, the EtOH is removed in vacuo and the residue treated with H<sub>2</sub>O, extd. with Et<sub>2</sub>O and the extract dried. III distils at 183-90.degree./1 mm. and then crystallizes, m. 70-2.degree.. The d-tartrate of III, after recrystn. (abs. EtOH) melts at 195.degree. (decompn.). I, after refluxing with p-chlorobenzhydryl chloride in PhMe in presence of NaHCO<sub>3</sub>, drying and treating with dry HCl gives the white solid N-(p-chlorobenzhydryl)-N'-carbethoxypiperazine-2HCl. This can be hydrolyzed and decarboxylated, by refluxing with concd. HCl, to the N-p-chlorobenzhydrylpiperazine (IV), b. 224.degree./1 mm. Benzhydrylpiperazines with the R1 = Me or Et may be prepd. by reacting the desired piperazine with HCHO (or its polymer) or MeCHO in conjunction with HCO<sub>2</sub>H. Thus 30 g. IV, 10.3 g. 35% HCHO, and 7.6 g. 90% HCO<sub>2</sub>H are heated 3 hrs. on a steam bath and then refluxed 4.5 hrs.; 7.7 g. concd. HCl is added and excess HCHO and HCO<sub>2</sub>H distd. in vacuo. The residue is dissolved in H<sub>2</sub>O and made alk. with aq. 40% NaOH. The sepd. oil is extd. 3 times with C<sub>6</sub>H<sub>6</sub>, the extracts concd., and the residue distd. N-(p-Chlorobenzhydryl)-N'-methylpiperazine (V) distd. at 178-81.degree./1 mm.; HCl salt, m. 221-2.degree.. The N'-ethylated roduct is prepd. similarly; the di-HCl salt, m. 227-8.degree.. Zn and HCl or Raney Ni in abs. EtOH may be used instead of HCO<sub>2</sub>H to reduce the aldehyde. The N'-alkylated compds. are useful in combating symptoms of histamine activity.</p>				
IT	111585-42-3, 1-Piperazinecarboxylic acid, 4-(p-chloro-.alpha.-phenylbenzyl)-, ethyl ester, dihydrochloride (prepn. of)				
RN	111585-42-3 CAPLUS				
CN	1-Piperazinecarboxylic acid, 4-(p-chloro-.alpha.-phenylbenzyl)-, ethyl ester, dihydrochloride (6CI) (CA INDEX NAME)				

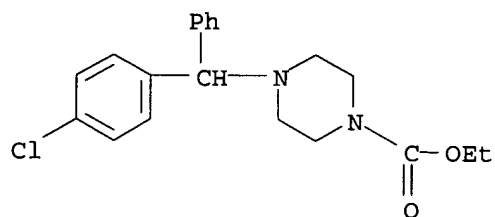
10/076448



●2 HCl

10/076448

L7 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2003 ACS  
AN 1958:24801 CAPLUS  
DN 52:24801  
OREF 52:4417e-g  
TI Nonaqueous titration of 1,4-disubstituted piperazines  
AU Ciaccio, L. L.; Missan, S. R.; McMullen, W. H.; Grenfell, T. C.  
CS Chas. Pfizer & Co., Inc., Brooklyn, NY  
SO Anal. Chem. (1957), 29, 1670-3  
CODEN: ANCHAM; ISSN: 0003-2700  
DT Journal  
LA Unavailable  
AB Potentiometric titrations of some 1,4-disubstituted derivs. with HClO4 in HOAc give 1 end point in HOAc solvent, but both end points in MeCN or MeNO2. The efficacy of 1,4-substituents in reducing strength decreases in the order EtOOC > Ph > p-chlorobenzhydryl > PhCH2, HOCH2CH2OCH2CH2, H. Thus, 4-substituted 1-carbethoxypiperazines are monobasic, 1,4-diphenylpiperazine gives 2 end points in HOAc and 1 in the weaker acid solvent MeNO2, and piperazine gives 1 end point corresponding to a dibasic base. By appropriate solvent choice differentiation according to base strength is possible.  
IT 80476-89-7, 1-Piperazinecarboxylic acid, 4-(p-chloro-.alpha.-phenylbenzyl)-, ethyl ester (titration of)  
RN 80476-89-7 CAPLUS  
CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, ethyl ester (9CI) (CA INDEX NAME)



L7 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2003 ACS

AN 1957:52175 CAPLUS

DN 51:52175

OREF 51:9717a-i,9718a-c

TI N,N'-Disubstituted-piperazines

PA Abbott Laboratories

DT Patent

LA Unavailable

FAN.CNT 1

S W

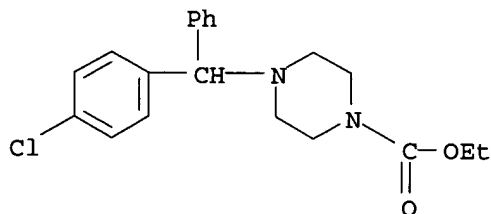
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	GB 752331		19560711	GB	
AB	<p>N,N'-Disubstituted-piperazines (I) were prepd. by treating Ph<sub>2</sub>CHCl or its substituted derivs. with substituted N-piperazines. Thus, refluxing and stirring a mixt. contg. 11.9 g. Ph(p-ClC<sub>6</sub>H<sub>4</sub>)CHCl, 50 g. N-methylpiperazine, and 5.3 g. Na<sub>2</sub>CO<sub>3</sub> in 75 ml. anhyd. xylene 60 hrs., extg. the hydrocarbon layer several times with dil. HCl, making the combined washings alk. with NaOH, extg. the oil with Et<sub>2</sub>O, drying, pptg. the di-HCl salt with gaseous HCl, and recrystg. from abs. EtOH-Et<sub>2</sub>O gave N-(p-chlorobenzhydryl)-N'-methylpiperazine, m. 220-1.degree.; HCl salt, m. 223-4.degree.. Similarly were prepd. the following I (N- and N'-substituents, b.p., and, in parentheses, salt formed and its m.p., given): Ph(p-BrC<sub>6</sub>H<sub>4</sub>)CH, Me, b0.5 161-71.degree. [di-HCl salt, 249-50.degree. (from abs. EtOH)]; Ph<sub>2</sub>CH, Me, - (m. 105-8.degree.) [di-HCl salt, 258-60.degree. (from abs. EtOH)]; Ph(p-MeOC<sub>6</sub>H<sub>4</sub>)CH, Me, b0.7 168-9.degree. [di-HCl salt, 194-5.degree. (from iso-PrOH-Et<sub>2</sub>O)]; (p-ClC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CH, Me, - [di-HCl salt, 245-6.degree. (from EtOH)]; Ph<sub>2</sub>CH, HOCH<sub>2</sub>CH<sub>2</sub>, - [di-HCl salt, 229.degree. (decompn.)]; Ph<sub>2</sub>CH, Et, - [di-HCl salt, 241.degree. (decompn.)]; Ph<sub>2</sub>CH, Me<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>, - [di-HCl salt, m. 255-7.degree. (decompn.) (from iso-PrOH-Et<sub>2</sub>O)]; Ph(p-IC<sub>6</sub>H<sub>4</sub>)CH, Me, b0.5 181.degree. (HCl salt, 260-1.degree.); .alpha.-(2-pyridyl)benzyl, Me, m. 95-7.degree.; Ph(p-FC<sub>6</sub>H<sub>4</sub>)CH, Me, b0.6 140-1.degree. (HCl salt, 230-1.degree.); Ph(p-MeC<sub>6</sub>H<sub>4</sub>)CH, Me, b1.0 159-60.degree. [HCl salt, 228-9.degree. (decompn.) (from abs. EtOH)]; C<sub>6</sub>H<sub>11</sub>(p-ClC<sub>6</sub>H<sub>4</sub>)CH, Me, - [di-HCl salt, 278-9.degree. (decompn.) (from EtOH)]; Ph(p-ClC<sub>6</sub>H<sub>4</sub>)CH, Et, - [di-HCl salt, 227.5-8.0.degree. (from EtOH-Et<sub>2</sub>O)]; Ph(o-ClC<sub>6</sub>H<sub>4</sub>)CH, Me, b2.0 179-80.degree. (HCl salt, 272-3.degree.); .alpha.-(2-thienyl)benzyl, Me, - [di-HCl salt, 202.degree. (decompn.) (from EtOH-pentane)]; Ph<sub>2</sub>CH, Bu, - [di-HCl salt, 248.degree. (decompn.) (from MeOHMe<sub>2</sub>CO)]; Ph(p-ClC<sub>6</sub>H<sub>4</sub>)CH, - [di-HBr salt, 253.5-5.0.degree. (from iso-PrOH)]; Ph(m-ClC<sub>6</sub>H<sub>4</sub>)CH, Me, b1.5 177.degree. [HCl salt, 249-50.degree. (from abs. EtOH)]; Ph<sub>2</sub>CH, HOCH<sub>2</sub>, - [HCl salt, 189-90.degree. (from EtOH-Et<sub>2</sub>O)]; .alpha.-(2-thienyl)-p-chlorobenzyl, Me, - [dioxalate, 216.degree. (decompn.)]; Ph(p-ClC<sub>6</sub>H<sub>4</sub>)CH, HO(CH<sub>2</sub>)<sub>4</sub>, - [di-HCl salt, 211-12.degree. (decompn.) (from EtOH-Et<sub>2</sub>O)]; Ph<sub>2</sub>CMe, Me, b0.7 162-5.degree. [di-HCl salt-H<sub>2</sub>O, 203-5.degree. (from abs. EtOH)]; Ph<sub>2</sub>CH, guanyl, - [H<sub>2</sub>SO<sub>4</sub> salt, 294-5.degree. (decompn.)]; Ph(p-ClC<sub>6</sub>H<sub>4</sub>)CH, Me, - [MeI salt, 119-20.degree. (decompn.) (from abs. EtOH)]; Ph(p-ClC<sub>6</sub>H<sub>4</sub>)CH, Me, b0.1 150-2.degree. [HCl salt, 223-4.degree. (decompn.)]. The following I were also prepd. (N- and N'-substituents shown; no phys. data reported): Ph<sub>2</sub>CH, iso-Pr; Ph<sub>2</sub>CH, iso-Bu; Ph<sub>2</sub>CH, HO(CH<sub>2</sub>)<sub>3</sub>; Ph<sub>2</sub>CH, Me<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>; Ph<sub>2</sub>CH, Me<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>; Ph<sub>2</sub>CEt, Me; Ph<sub>2</sub>CBu, Me; (p-IC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CH, Me; (o-ClC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CH, Me; p-ClC<sub>6</sub>H<sub>4</sub>(p-BrC<sub>6</sub>H<sub>4</sub>)CH, Me; p-BrC<sub>6</sub>H<sub>4</sub>(p-MeOC<sub>6</sub>H<sub>4</sub>)CH, Me; p-ClC<sub>6</sub>H<sub>4</sub>(p-MeC<sub>6</sub>H<sub>4</sub>)CH, Me; (p-MeC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CH, Me; (p-MeOC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CH, Me; .alpha.-cyclopentylbenzyl, Me; .alpha.-(2-pyrimidyl)benzyl, Me; .alpha.-(2-furyl)benzyl, Me; Ph(p-ClC<sub>6</sub>H<sub>4</sub>)CH, EtO<sub>2</sub>C. Intermediates for the prepn. of I by alternative methods are given. Thus, refluxing 29.8 g. N-carbethoxypiperazine, 46.5 g. Ph<sub>2</sub>CHBr, and 21.2 g. Na<sub>2</sub>CO<sub>3</sub> in 125 ml. xylene gave N-benzhydryl-N'-carbethoxypiperazine(II), m. 114-15.degree.. Refluxing 14 g. II and 56 g. KOH in 250 ml. 95% EtOH 22 hrs., concg. in vacuo, treating the residue with H<sub>2</sub>O, extg. with Et<sub>2</sub>O,</p>				

drying, and distg. gave N-benzhydrylpiperazine, b1.0 183-90.degree., which crystallizes and m. 70-2.degree.; d-tartaric acid salt, m. 195.degree. (decompn.) (from abs. EtOH). Refluxing 47.4 g. N-carbethoxypiperazine, 32.6 g. Cl(CH<sub>2</sub>)<sub>4</sub>OH, and 31.8 g. Na<sub>2</sub>CO<sub>3</sub> in 150 ml. anhyd. EtOH 5 hrs. gave N-carbethoxy-N'-(4-hydroxybutyl)piperazine (III), b0.4 165-8.degree. (HCl salt, m. 118-19.degree.). Hydrolyzing 24 g. III in 100 ml. concd. HCl gave N-(4-hydroxybutyl)piperazine, b6.0 142.degree.. Dissolving 82 g. Ph(p-FC<sub>6</sub>H<sub>4</sub>)CHOH in 50 ml. C<sub>6</sub>H<sub>6</sub> and 50 ml. n-hexane, mixing with excess CaCl<sub>2</sub>, treating with HCl, cooling, keeping the temp. at 12-25.degree., pouring the soln. over a fresh batch of CaCl<sub>2</sub>, repeating in 15 min., filtering, concg., and distg. the residue gave Ph(p-FC<sub>6</sub>H<sub>4</sub>)CHCl, b1.0 125-7.degree.. Similarly Ph(p-IC<sub>6</sub>H<sub>4</sub>)CHCl, b0.6 148-9.degree., was prepd.

Treating a cooled mixt. of 24 g. .alpha.-(2-pyridyl)benzhydryl alc. HCl salt in 200 ml. anhyd. C<sub>6</sub>H<sub>6</sub> with 36 g. SOCl<sub>2</sub>, stirring 1 hr., allowing to stand at room temp. 15 hrs., heating 1 hr. at 60.degree., concg. in vacuo, removing the excess SOCl<sub>2</sub> by repeated addn. of anhyd. C<sub>6</sub>H<sub>6</sub>, distg. in vacuo, dissolving the residue in H<sub>2</sub>O, making alk. with Na<sub>2</sub>CO<sub>3</sub>, extg. with Et<sub>2</sub>O, and distg. gave .alpha.-(2-pyridyl)benzhydryl chloride, b0.3 126-31.degree.. Refluxing 23.7 g. Ph(p-ClC<sub>6</sub>H<sub>4</sub>)CHCl, 10.5 g.

(HOCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>NH, and 10.6 g. Na<sub>2</sub>CO<sub>3</sub> in 150 ml. dry PhMe 40 hrs., decanting the supernatant liquid, concg., and distg. the yellow oil gave Ph(p-ClC<sub>6</sub>H<sub>4</sub>)CHN(CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>, b0.1 197-207.degree. (HCl salt, m. 135-7.degree.. Adding 70.3 g. p-ClC<sub>6</sub>H<sub>4</sub>CHO to a Grignard reagent prepd. from 114.1 g. cyclohexyl bromide and 14.4 g. Mg, decomp. the addn. complex with NH<sub>4</sub>Cl, extg. with Et<sub>2</sub>O, and distg. gave the carbinol, b0.7 122-5.degree., which on standing solidifies and m. 70-1.degree.; treatment with HCl gave .alpha.-cyclohexyl-p-chlorobenzyl chloride, b1.6 134-6.degree.. Similarly prepd. was the .alpha.-(2-thienyl) analog which decomp. on heating. Adding 45 g. MeCPh<sub>2</sub>CONH<sub>2</sub> to an alk. hypobromite soln. prepd. from 33.6 g. Br and 82 g. KOH in 425 ml. cold H<sub>2</sub>O, stirring 1 hr. at 0.degree., gradually warming to room temp., then on a steam bath 30 min., extg. the yellow oil with Et<sub>2</sub>O, drying, concg., and distg. the residue gave MeCPh<sub>2</sub>NH<sub>2</sub>, b4 140-2.degree.; HCl salt, m. 245-6.degree.. Refluxing 33 g. N-carbethoxy-N'-butylpiperazine in 170 ml. concd. HCl 42 hrs., concg. in vacuo, dissolving the residue in warm H<sub>2</sub>O, making alk. with 50% KOH, extg. the oil layer with Et<sub>2</sub>O, drying, and distg. gave N-butylpiperazine, b747 192-5.degree.. The compds. are useful in combating symptoms of histamine and have antispasmodic activity.

- IT 80476-89-7, 1-Piperazinecarboxylic acid, 4-(p-chloro-.alpha.-phenylbenzyl)-, ethyl ester  
(prepn. of)  
RN 80476-89-7 CAPLUS  
CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, ethyl ester (9CI) (CA INDEX NAME)



10/076448

L7 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2003 ACS

AN 1957:30115 CAPLUS

DN 51:30115

OREF 51:5847a-b

TI N-Diarylmethylpiperazines

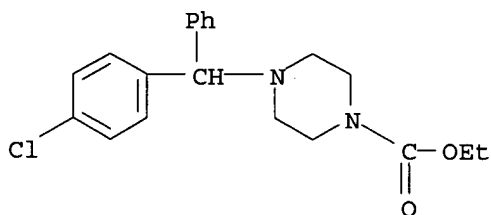
PA Abbott Laboratories

DT Patent

LA Unavailable

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	GB 752332		19560711	GB	
GI	For diagram(s), see printed CA Issue.				
AB	N-Diarylmethyl-N'-carbalkoxypiperazines were hydrolyzed and decarboxylated by refluxing with concd. HCl or KOH in EtOH. Thus, p-ClC <sub>6</sub> H <sub>4</sub> PhCHN.(CH <sub>2</sub> ) <sub>2</sub> N(CO <sub>2</sub> Et).CH <sub>2</sub> .CH <sub>2</sub> , prepd. from N-carbethoxypiperazine and 4-ClC <sub>6</sub> H <sub>4</sub> PhCHCl refluxed with concd. HCl gave N-p-chlorobenzhydrylpiperazine. Similarly, N-benzhydryl-N'-carbethoxypiperazine refluxed 22 hrs. in KOH-EtOH gave benzhydrylpiperazine, b1 183-90.degree., m. 70-2.degree..				
IT	80476-89-7, 1-Piperazinecarboxylic acid, 4-(p-chloro-.alpha.-phenylbenzyl)-, ethyl ester (and its decarboxylation)				
RN	80476-89-7 CAPLUS				
CN	1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, ethyl ester (9CI) (CA INDEX NAME)				



*Sam*

10/076448

=> file caold

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

92.81

259.33

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE

TOTAL

ENTRY

SESSION

CA SUBSCRIBER PRICE

-13.02

-13.02

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FILE COVERS 1907-1966

FILE LAST UPDATED: 01 May 1997 (19970501/UP)

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L3 7 S L2

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L5 4 S L4

L6 43 S L4 SSS FULL

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L7 20 S L6

FILE 'CAOLD' ENTERED AT 17:58:38 ON 02 JUN 2003

=> s l6

L8 7 L6

=> d l8 1-7 bib hitstr

10/076448

L8 ANSWER 1 OF 7 CAOLD COPYRIGHT 2003 ACS

AN CA54:12169h CAOLD

TI substituted methylpiperazines

AU Janssen, Paul A. J.

DT Patent

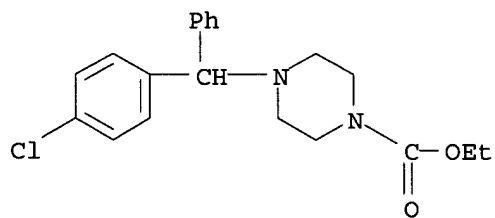
PATENT NO.	KIND	DATE
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PI BE 539693

IT 80476-89-7

RN 80476-89-7 CAOLD

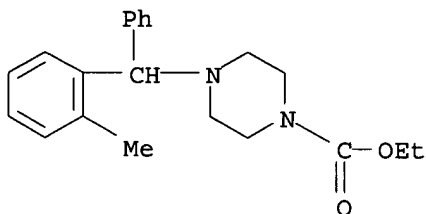
CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, ethyl ester (9CI) (CA INDEX NAME)



*Patent*  
*Saw*  
*teachers only & test.*

10/076448

L8 ANSWER 2 OF 7 CAOLD COPYRIGHT 2003 ACS  
AN CA53:21986f CAOLD  
TI unsymmetrically substituted piperazines - (XII) benzhydrylpiperazines and  
related compds. with spasmolytic and antifibrillatory action  
AU Ide, Walter S.; Lorz, E.; Phillips, A. P.; Russell, P. B.; Baltzly, R.;  
Blumfeld, R.  
IT 112350-85-3  
RN 112350-85-3 CAOLD  
CN 1-Piperazinecarboxylic acid, 4-(o-methyl-.alpha.-phenylbenzyl)-, ethyl  
ester, hydrochloride (6CI) (CA INDEX NAME)



● HCl

10/076448

L8 ANSWER 3 OF 7 CAOLD COPYRIGHT 2003 ACS

AN CA53:7215f CAOLD

TI piperazine derivs.

AU Weston, Arthur W.; Hamlin, K. E.

PA Abbott Laboratories

DT Patent

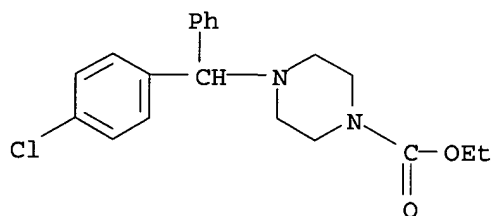
PATENT NO.	KIND	DATE
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PI	US 2861072	1958
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IT 80476-89-7

RN 80476-89-7 CAOLD

CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, ethyl ester (9CI) (CA INDEX NAME)



10/076448

L8 ANSWER 4 OF 7 CAOLD COPYRIGHT 2003 ACS

AN CA52:15598e CAOLD

TI benzhydryl carbalkoxy piperazines

AU Weston, Arthur W.; Hamlin, K. E.

PA Abbott Laboratories

DT Patent

PATENT NO.	KIND	DATE
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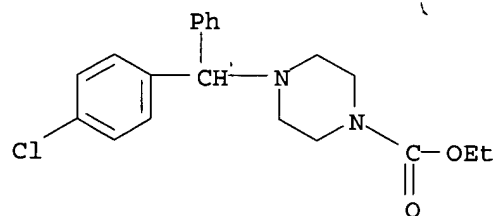
PI	US 2819269	1958
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IT 111585-42-3

RN 111585-42-3 CAOLD

CN 1-Piperazinecarboxylic acid, 4-(p-chloro-.alpha.-phenylbenzyl)-, ethyl ester, dihydrochloride (6CI) (CA INDEX NAME)

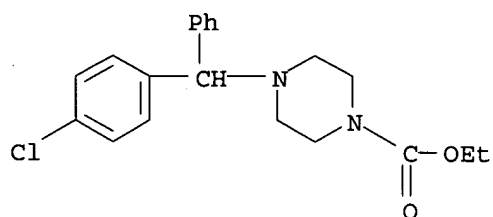
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●2 HCl

10/076448

L8 ANSWER 5 OF 7 CAOLD COPYRIGHT 2003 ACS  
AN CA52:4417f CAOLD  
TI nonaq. titration of 1,4-disubstituted piperazines  
AU Ciaccio, L. L.; Missan, S. R.; McMullen, W. H.; Grenfell, T. C.  
IT 80476-89-7  
RN 80476-89-7 CAOLD  
CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, ethyl ester (9CI) (CA INDEX NAME)



10/076448

L8 ANSWER 6 OF 7 CAOLD COPYRIGHT 2003 ACS

AN CA51:9717a CAOLD

TI N,N'-disubstituted-piperazines

PA Abbott Laboratories

DT Patent

PATENT NO. KIND DATE

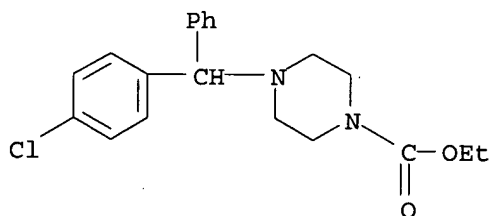
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PI GB 752331

IT 80476-89-7 111585-42-3

RN 80476-89-7 CAOLD

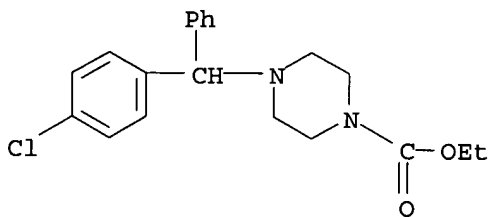
CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, ethyl ester (9CI) (CA INDEX NAME)



*Saw*

RN 111585-42-3 CAOLD

CN 1-Piperazinecarboxylic acid, 4-(p-chloro-.alpha.-phenylbenzyl)-, ethyl ester, dihydrochloride (6CI) (CA INDEX NAME)



● 2 HCl

10/076448

L8 ANSWER 7 OF 7 CAOLD COPYRIGHT 2003 ACS

AN CA51:5847a CAOLD

TI N-diarylmethylpiperazines

PA Abbott Laboratories

DT Patent

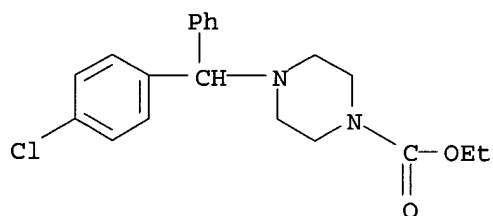
PATENT NO.	KIND	DATE
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PI GB 752332

IT 80476-89-7

RN 80476-89-7 CAOLD

CN 1-Piperazinecarboxylic acid, 4-[(4-chlorophenyl)phenylmethyl]-, ethyl ester (9CI) (CA INDEX NAME)



See

10/076448

=> log h

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
18.74	278.07

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
0.00	-13.02

CA SUBSCRIBER PRICE

SESSION WILL BE HELD FOR 60 MINUTES

STN INTERNATIONAL SESSION SUSPENDED AT 17:59:23 ON 02 JUN 2003